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An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

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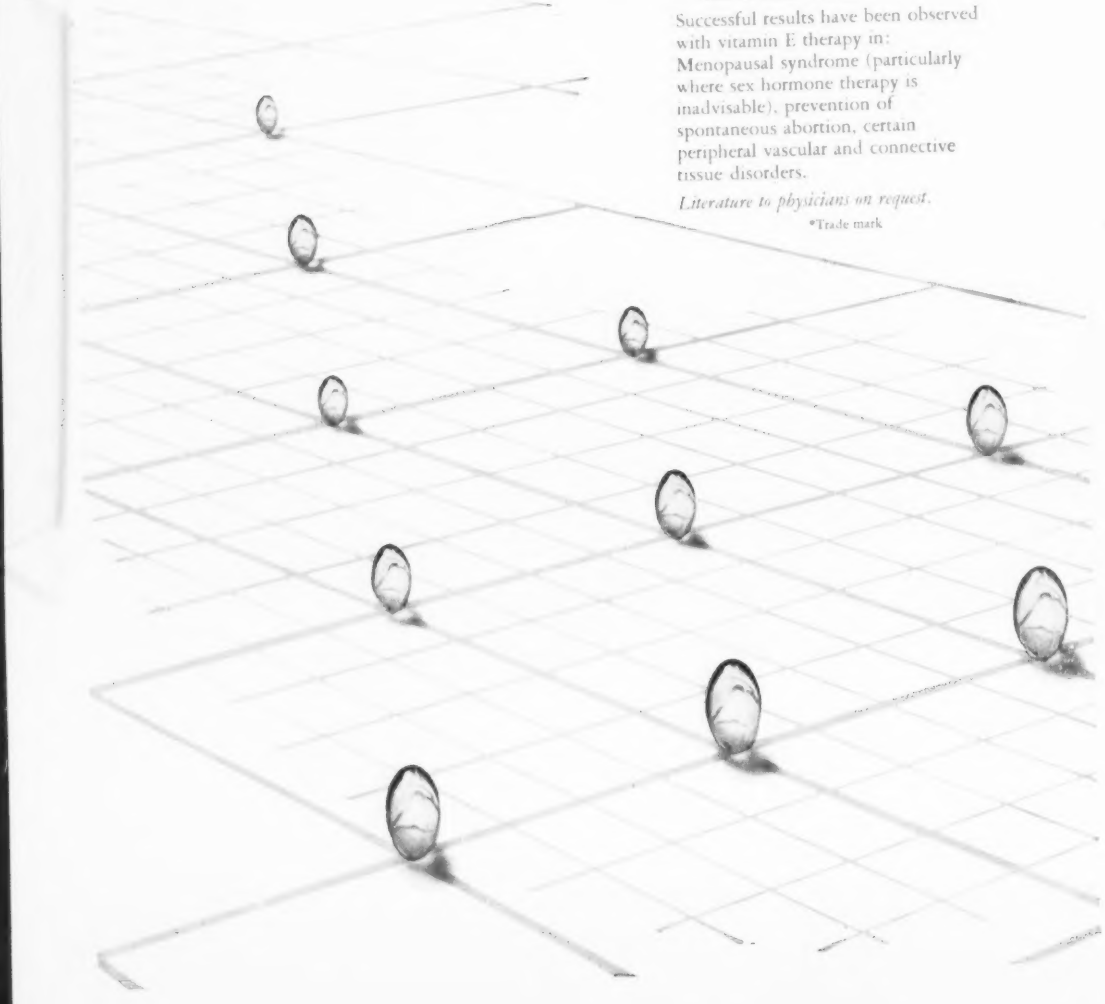

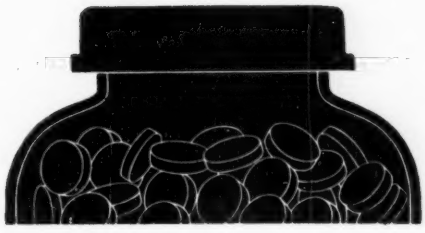

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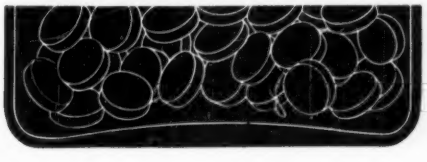

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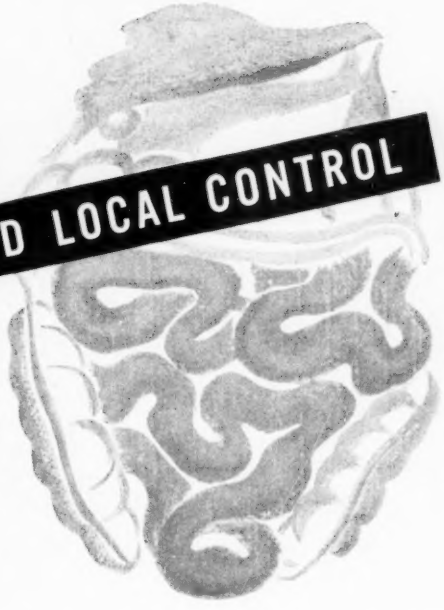

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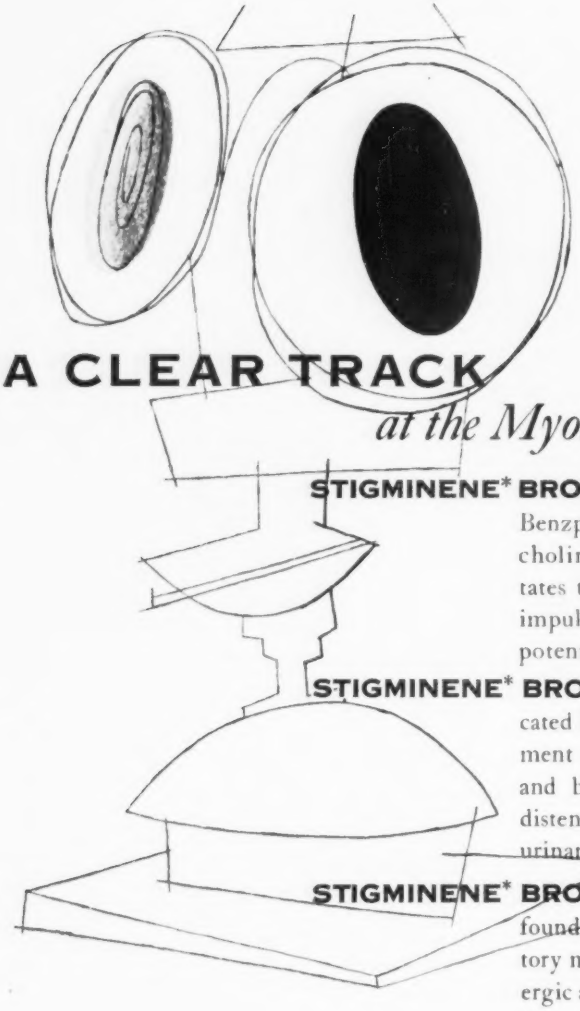

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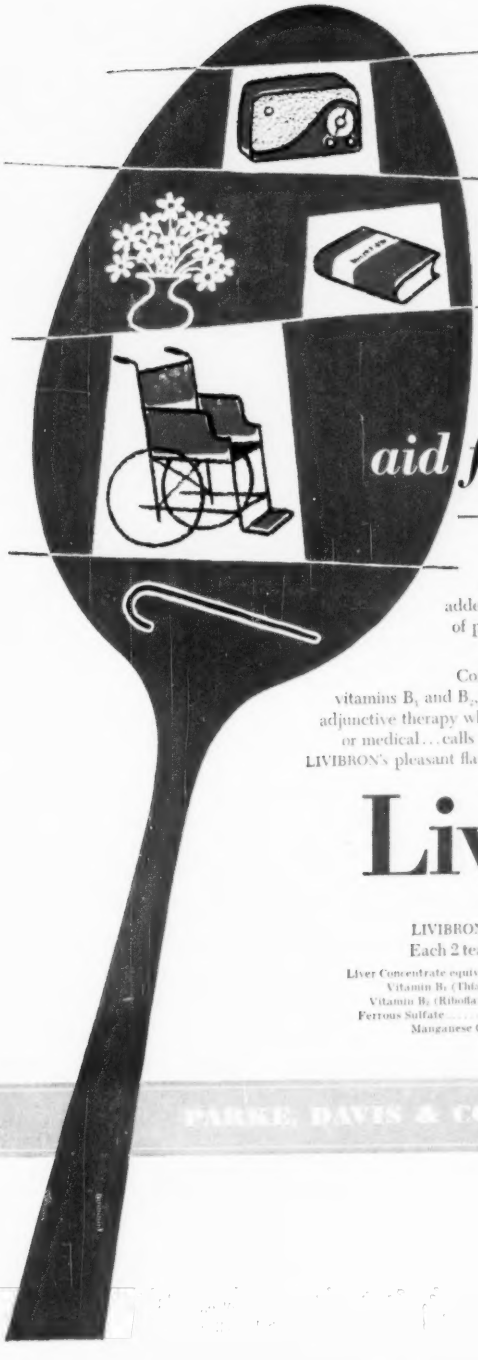

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Turn out again onto floured board and knead lightly about 2 minutes. Shape dough into 2 loaves. Place into lightly greased bread pans (8 x 4 x 3 inches). Cover and let rise again until double in bulk (about 1 hour).

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DYSFUNCTIONING, NON-CALCULOUS GALLBLADDER

JAMES F. CRENSHAW, M. D., Birmingham, Ala.*

THE cholecystographic finding of the gallbladder with normal dye concentration but sluggish emptying (without other evidence of abnormality) is a problem of great interest and magnitude both to the gastroenterologist and surgeon. Probably in no other abnormality of the biliary system must such care in final judgment be exercised as in the proper diagnosis and therapy of this functional disorder. A study of 500 consecutive cholecystograms has shown 107 gallbladders (21%) falling into this group. This figure compares favorably with Feldman's (1) who analyzed 396 consecutive cases and found an incidence of 19%. It is generally recognized in individuals of apparently normal health that both functional and pathological changes may be present in the gallbladder; also, that 10% of routine examinations (asymptomatic) reveal a dysfunctioning, sluggish-emptying gallbladder. Carter, et al, (2) observed that approximately 70% of those manifesting typical gallbladder symptoms showed no evidence of stones, but exhibited gallbladders capable of normally concentrating the dye without adequate power of evacuation. In this report there was no case without some form of digestive disturbance.

Although many reports are available concerning the dysfunctioning gallbladder, no exact criterion of emptying has been set forth. It is usually held, however, that at least 50% emptying should take place by three hours following the fat meal. A normal gallbladder, as a rule, contracts to half or less within 30 minutes following a fat meal. The purpose of this presentation is an attempt to evaluate the significance of the dysfunctioning, non-calculous gallbladder from the clinical standpoint, both diagnostically and therapeutically.

Because of the functional nature of this biliary disorder, the physiology of the region must be briefly considered. Under normal conditions the gallbladder fills only when the sphincter of Oddi is closed and empties only when this sphincter opens. In addition to the function of bile storage, the gallbladder regulates the extra-hepatic biliary pressure. The average capacity of the gallbladder is 40 cc., while the liver secretes about 700 cc. of bile daily. When the gallbladder contracts against a closed sphincter of Oddi, the high secretory pressure of the liver blocks the passage of bile back into the hepatic radicles. The significance of the gallbladder in regulating the extra hepatic biliary pressure is readily observed following cholecystectomy when the daily output of bile is secreted against the sphincter of Oddi. With contraction of the gallbladder a few minutes following the ingestion of a fat stimulus, relaxation of the neck, cystic and common ducts takes place and the sphincter of Oddi opens allowing free ingress of bile into the duodenum. Delayed emptying of the gallbladder may be produced by a spastic sphincter mechanism. It has been shown that at times a distended gallbladder will not release its contents following spontaneous or artificial opening of the sphincter of Oddi. It is well known that among the foods, fat is the greatest stimulant to gallbladder contraction; meat and peptone proteins are inferior to fats in this regard, but superior to carbohydrates which produce little or no emptying response. Cholecystokinin, the hormone obtained from the mucosa of the duodenum and upper jejunum, is a powerful stimulant to gallbladder contraction; dilute hydrochloric acid in the duodenum excites the production of this hormone. Although several other factors, including the extrahepatic biliary sphincters, intra-abdominal pressure, the flushing, milking, postural and gravity influences, play a role in the evacuation of the gallbladder, it remains that the greatest influence is exerted by the humoral and reflex nervous mechanisms (cephalic and gastro-intestinal). Segal, et al, (3) describe the expulsion of bile from the gallbladder in two phases: 1) cephalic phase—under nervous control, short in duration; 2) hormonal phase—cholecystokinin, secreted from the duodenum by fat stimulus, and more prolonged than phase one.

The subserous zone of the gallbladder wall with its lymphatic and blood supply is responsible for the concentration of the bile. The fibromuscular layer's elasticity is an important factor in the emptying and refilling of the gallbladder; intrinsic pathological changes of this structure may damage distensibility and contractility.

Concerning the factors responsible for delayed emptying of the gallbladder, it is obvious that derangements of any of the normal evacuating mechanisms might produce this condition. Abnormally thick mucus or bile will stagnate the flushing of the gallbladder. Deficiencies of cholecystokinin also play a significant role in the emptying power. Among other intrinsic causes are damage to the fibromuscular wall of the gallbladder, kinking of the neck, spasm of the cystic duct, dysfunction of the reciprocal mechanism of gallbladder and sphincter of Oddi, reflex and nerve abnormalities. Chief among the extrinsic causes are disturbances within the gastro-intestinal tract such as hypochlorhydria, pyloric spasm or obstruction, peptic ulcer and ileus. Pregnancy has been shown to prolong the evacuation, also hypothyroidism and allergy. Drugs such as morphine, codeine, dilaudid and pantopon will inhibit the flow of gallbladder bile by producing a spasm of the sphincter at the distal common duct, resulting in an increase in biliary pressure.

ANALYSIS OF CLINICAL FINDINGS

Abdominal discomfort (no localization)	69
Epigastric discomfort radiating to back and/or subscapular area	29
Acute gallbladder attack	12
Abdominal distention—gas	63
Burning discomfort	44
Nausea	44
Vomiting	28
Appetite	good 61, poor 38

*From the Department of Gastro-enterology, Seale Harris Clinic, Instructor in Medicine, Medical College of Alabama.

Food effect	relief 13, worse 32, no effect 51	
Hypoacidity (under 15° HCl)		
	(from 69 gastric analyses)	25
Bowel	irregular 7, diarrhea 4, constipated	54
Icterus		8
Hepatomegaly		3
Chills and fever		2
Obesity (more than 15 lbs. overweight)		9
Normal weight		19
Overweight		17
Underweight		71
BMR (total performed 54)		
	normal range 23, hyper 4, hypo	27
Allergy		1
Gastro-intestinal studies		93
Negative		63
Hypertonic upper G-I tract		67
Irritable, spastic colon		16
Peptic ulcer	gastric 0, duodenal	4
Genito-urinary tract		3
Renal calculi		3
Operations		44
Appendectomy		26
Gynecological		16
Genito-urinary		1
Thyroid		1

Of the 107 cases of sluggish-emptying gallbladders analyzed, there was none without some form of digestive complaint. Typical gallbladder symptoms were manifested by 38, while digestive disturbances other than typical gallbladder type were seen in 69.

Ages ranged from 15 to 73, the majority falling in the sixth decade. There were 65 females and 42 males. The endocrine and post-pregnancy factors are probably responsible for the sex distribution.

Only 12 had typical attacks of acute gallbladder disease, while 29 showed epigastric discomfort radiating to the back. Abdominal discomfort without localization was experienced by 69. A significant number exhibited the common digestive disturbances of gas, burning, nausea and constipation. Intake of food relieved 13, made 32 worse, and had no effect in 51.

Obesity (over 15 lbs. overweight) was shown by only 9; however, 17 were overweight as determined by the standard height-age-weight charts. Nineteen were normal weight. Seventy-one were classified as underweight.

A total of 54 basal metabolism studies were performed. Using +10% to —10% as the normal range, 23 were normal, 4 were hypermetabolic and 27 hypometabolic. From observations on thyroid function as a factor in gallbladder disease and formation of gallstones, Simendinger (4) concluded that hypothyroidism is an important factor in gallbladder function in that large quantities of debris and concretions, in addition to positive roentgen findings, point to a considerable degree of stasis within the gallbladder. He further found that high blood cholesterol did not produce high cholesterol content of hepatic bile or deposition of cholesterol in the gallbladder wall. He is of the opinion that a constitutional disease as hypothyroidism, because of stasis production, renders the gallbladder more liable for bacterial invasion.

Sixty-nine gastric analyses were performed on individual subjects, 25 disclosing definite hypochlorhydria (below 15° free HCl). Fasting and post-alcohol stimulant specimens were used.

Ninety-three of the 107 cases were studied by roentgen examination of the gastro-intestinal tract. Sixty-three were negative for actual intrinsic pathological lesions. Sixty-seven revealed some degree of hypertonicity. An irritable, spastic colon was thought to be present in 16 cases. Duodenal ulcer was found in 4 cases, but no gastric ulcer was disclosed. In Feldman's (5) analysis of 115 cases of peptic ulcer, 10.4% showed abnormal dye filling during the cholecystogram and 27.3% a sluggish or non-contracting gallbladder. No cases of malignancy occurred throughout the series. Three patients had renal calculi.

Forty-four individuals had been subjected to operations, the majority having appendectomies and gynecological surgery. In no case in this series to this date has surgery been required for the gallbladder.

Feldman's (1) series of 75 cases of sluggish-emptying gallbladder was divided into 27 normal tone, 28 hypertonic, and 20 hypotonic. Carter's (2) group showed 25% hypertonic and 15% hypotonic. In comparing the average contraction of his normal series with the sluggish group, Feldman found that the normal gallbladder contracts almost three times greater in the transverse dimension and slightly over twice in length.

It is well to remember, at this point, in the discussion of functional disorder of bile flow that the term "biliary dyskinesia" (referring to interference with bile flow into the duodenum as a result of spasm of the sphincter of Oddi) is more wisely used with reference to post-cholecystectomy and disease states rather than with purely functional disorders. It is true, however, that such a condition does exist functionally, but admittedly quite rarely.

The management of gallbladder disease in general is controlled largely by three main factors: 1) etiological basis—infection, stasis, metabolic abnormalities; 2) cholecystographic findings; 3) clinical manifestations with proper evaluation from both the medical and surgical viewpoints. Casellas (6) is of the belief that a good concentration of dye within the gallbladder does not eliminate gallbladder pathology unless the shadow disappears or almost disappears three hours after the fat meal. He cites the strawberry gallbladder as an example of intrinsic gallbladder disease with a hyperdense dye shadow. He holds, also, that a retention of more than 50% of dye after the fat meal, following adequate medical treatment with persisting symptoms, is a clear indication for surgical intervention. Adhesions or cystic duct changes were reported by Cole and Rossiter (7) in their operated cases having normal dye concentration but sluggish emptying. In reviewing the post-operative courses of the sluggish emptying group, Hellstrom (8) observed 30% and Doubilet (9) 40% had recurrence of symptoms similar to their preoperative state.

In the great majority of the sluggish evacuators it would seem that a conservative medical regime is the favored course of treatment. Attention is directed to stimulating a more normal biliary flow throughout the system with attempts to flush the gallbladder of stagnant bile and at the same time influence the content of gallbladder bile toward the normal. In the non-functioning gallbladder stasis is a major problem and must be

altered. Stasis does not play such a significant role in the functioning organ for the abnormality lies chiefly within the bile content. Non-surgical drainage of the gallbladder continues to be of help in the conservative handling of such cases. Morrison, et al, (10) have shown that ox bile may favorably alter the chemistry of bile by reduction in the content of solids, lipids and mucin, exerting a possible prophylactic effect against calculi formation. Bile salt therapy, using ox bile, is of benefit, if used in adequate amounts, as it renders more normal the ingress and egress of the bile flow; the chemistry, including the PH, is also favorably influenced. From their experiments in animals and in vitro, Morrison and Feldman (11) have shown that circulating bile works as a prophylactic agent in the prevention of gallstones. If the therapeutic aim is to flush the bile duct with a free-flowing, thin bile, an oxidized unconjugated preparation as dehydrocholic acid is administered; if the purpose is to increase the volume output of liver bile and the bile salt content, then a "natural ox bile salts" is given (12). Decholin (dehydrocholic acid produced by oxidation of cholic acid derived from bile) and Ketochol (oxidized or Keto form of all four bile acids—cholic, desoxycholic, chenodesoxycholic and lithocholic—normally present in human bile) are hydrocholeretic agents which stimulate the drainage of the bile ducts by enhancing the biliary flow over 100%.

The diet should not be completely fat free, as a certain amount is indicated to stimulate the emptying mechanism of the gallbladder. As function returns toward normal, a gradual increase in fatty foods is allowed. Those with hypertonicity are relaxed from antispasmodics such as atropine or trasentine. The hypochlorhydria group needs dilute hydrochloric acid. Thyroid is, of course, administered in proper dosage to the hypothyroid cases. Elimination of all extrinsic factors should be attempted. Surgery is indicated only when strict, conservative medical care is repeatedly without benefit.

Conclusions

1. The incidence of the normal concentrating sluggish-emptying gallbladder is high, there being 107 (21%) from 500 consecutive cholecystograms studied.

2. The entire group of 107 cases showed some form of digestive disturbance, although only 35% showed typical gallbladder symptoms.

3. Abdominal discomfort without localization was found in 64%, while epigastric discomfort radiating to the back was seen in only 27%. Only 11% experienced actual acute gallbladder attacks.

4. Extrinsic factors, in addition to intrinsic causes, play a significant role in the sluggish emptying of a normal concentrating gallbladder. The gastro-intestinal tract is the chief offender.

5. Gastric hypochlorhydria (under 15° HCl) was found in 36% of 69 gastric analyses performed.

6. Fifty per cent of 54 basal metabolism tests proved to be hypometabolic.

7. Sixty-six per cent were underweight, while 16% were overweight with only 8% actually obese.

8. Treatment in each case has been medical without surgical intervention. Surgery, it is believed, is indicated only after all conservative medical measures have failed.

9. Dysfunctioning of the gallbladder is conceivably the initiating step progressing into true non-functioning and actual cholecystitis.

10. Three, five and ten year follow-ups will probably reveal significant findings as to the progressive nature of gallbladder disease.

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GASTRIC RESIDUE IN CHOLECYSTOGRAPHY

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THE significance of a 6 hour gastric residue in the routine gastro-intestinal series is generally appreciated. The importance of finding residual contrast media in the stomach during cholecystography has to this point escaped attention. Our attention was first attracted to this problem early in 1948, when during a routine cholecystographic examination a pea-sized fleck of contrast media was noted in the region of

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the bulb. Clinically, the patient's symptoms were strongly suggestive of biliary disease. However, because of the normal gall bladder visualization and the pea-sized fleck in the bulb, a gastro-intestinal series was requested. This confirmed our impression of a duodenal ulcer. About 30% gastric residue was present.

HISTORICAL

Graham & Cole in 1924 were the first to demonstrate the gall bladder radiographically, utilizing the discovery of Abel & Rowntree (1910), that halogenated phenolphthalein derivatives were excreted by the liver and concentrated in the gall bladder. The gall bladder dye is absorbed through the mucosa of the small intestines, entering the portal blood stream. It is then carried to the liver, where the hepatic cells excrete it with the bile. Together they pass it through the branches of the biliary duct system to the gall bladder, when it is concentrated 6 to 10 times. Sufficient dye is present to render the gall bladder opaque. The dye-laden bile enters the duodenum through the common bile duct, and part of the dye then is re-absorbed via the enterohepatic cycle.

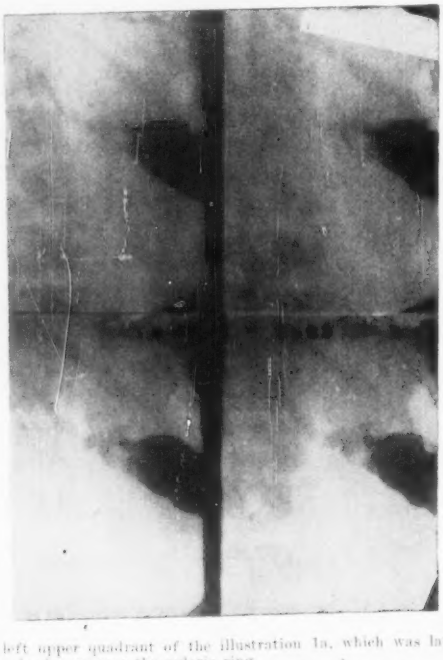
Priodax, beta-(4-hydroxy-3 5-diiodophenyl)-alpha-phenyl propionic acid, is not a phenolphthalein derivative, nor a dye. It contains 51.37% iodine. Feldman, as well as Wasch, describe priodax as being completely and rapidly absorbed in the intestinal tract, transported through the portal circulation to the liver, from whence it is excreted into the bile radicals, collecting in the gall bladder.

Six to twelve tablets of priodax are taken during or shortly after a fat free meal in the evening. It reaches the stomach in its water insoluble acid form. *In the stomach no absorption occurs.* In the duodenum pancreatic and intestinal secretions bring the pH of the duodenal contents to 6 or 7. The alkaline pH is favorable to the formation of soluble salts of priodax. As it progresses in the small intestines the conditions are more and more favorable to its solution the gradient in pH increasing from 6.5 in the duodenum to 8 in the last ileal loops. The added bile in the intestines has a twofold effect. It increases the solubility of priodax and facilitates its absorption. That priodax is unchanged by the process of absorption is shown by unchanging iodine content in ultrafiltration experiments. About four-fifths is eventually excreted by the kidneys, one-fifth is excreted with the feces.

Intestinal absorption reaches its maximum 3-4 hours when ingested after a meal. None is absorbed in the stomach. Hence any pathological condition delaying gastric evacuation interferes with the concentration of sufficient priodax to permit a definite interpretation with respect to the status of the gall bladder. On the other hand the gastric residue should direct the roentgenologist's attention to the stomach and/or duodenum as the site of the important pathological entity. This is especially significant when one realizes that the residue observed is at least 14 hours in duration.

CASE REPORTS

Case 1. This is the case mentioned in the introduction. The patient was admitted with a clinical impression of biliary disease. Cholecystography revealed a functionally competent gall bladder with no evidence of lithiasis. In view of the pea-sized static fleck in the bulb, a gastro-intestinal series was advised, which revealed a duodenal ulcer, with partial obstructive tendency.



Figs. 1a, b. Case H. L. L. Gastric residue of priodax is observed in the left upper quadrant of the illustration 1a, which was later shown to be secondary to an ulcer of the duodenum near the pyloric ring.

Case 2 (fig. 1) L. L., a 51 year old female, a known hypertensive with a past history of a stroke, was admitted to the hospital on Aug. 6, 1948, complaining of abdominal pain. There was an 8 year history of fatty and fried food intolerance. Two days prior to admission she ate soft shell crabs, after which she developed right upper quadrant pain, at first colicky, and later stabbing in character, associated with repeated vomiting. She had a chill the day before admission, followed by a temperature of 104. Urine was dark.

Further history was non-contributory.

Pertinent physical findings—The patient was an obese middle aged woman, in moderate distress. T104 P130 R22. Isolated neurological findings were present, residual from an antecedent left sided hemiplegia of a half year ago. Abdominal examination revealed right upper quadrant tenderness. The liver and gall bladder were not palpable. Nor were there any masses.

Laboratory reports: CBC R. B. C. 4,640,000, Hb. 12gm, W.B.C. 14,300, neutrophiles 84, lymphocytes 12, monocytes 4. Urinalysis—Specific gravity 1.022, protein 1, bile slightly positive, 5 W. B. C. per HPF, a few casts, many epithelial cells, an occasional R. B. C. Sed. rate 56 mm/hr. Liver function tests: Icteric Index 100 units. Cephalin Cholesterol Flocculation negative. Thymol turbidity 1.0 unit. Urobilin 45.3mg/24 hrs. Bile pigment faintly positive. Chemical examination of the blood:—N. P. N. 38.0 mg %, alkaline phosphatase 4.2 units, true glucose 60mg%. Wassermann negative. Stools faintly positive for occult blood.

The clinical diagnosis was acute cholecystitis with cholelithiasis, and was treated conservatively with the use of penicillin and streptomycin, on which regime the patient improved.

X-Ray Examination

Chest—8/7/48—enlarged hypertensive heart.

Gall bladder series—Non visualization of the gall bladder. "Contrast media is observed in the stomach 18 hours after the administration of priodax, and again on the following day after the administration of the second dose. The lack of visualization of the gall bladder may be due to the lack of absorption, rather than a pathological gall bladder even though a double dose of dye was administered. A definite conclusion cannot at the moment be given. Of major importance, however, is the evidence of obstruction in the pyloro-duodenal area. A gastro-intestinal series is advised."

G. I. Series—8/18/48—Marked pyloric obstruction due to ulcer.

The patient wished to go home. She was advised that surgery was indicated, but refused. She was sent home on an ulcer regime. The final diagnosis was: Obstructive duodenal ulcer; hypertensive cardiovascular disease with left partial hemiplegia.

Comment: The clinical diagnosis of acute cholecystitis was changed to obstructive duodenal ulcer as a result of observing gastric residue of priodax 18 hours after ingestion. A casual interpretation might have substantiated the clinical impression, in view of the non-visualization of gall bladder. In reality, whether biliary disease is co-existent with the ulcer cannot absolutely be determined.

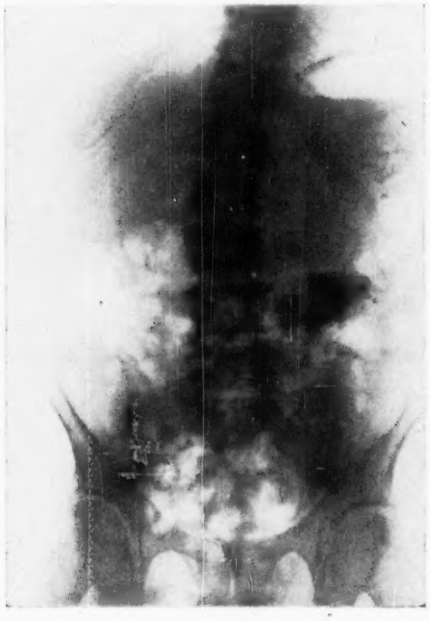
Case 3 (fig. 2) J. W., a 63 year old male, admitted to the hospital with intermittent bilateral flank pain of five years duration. The pain was more marked on the left side, radiating to the back, and not associated with meals. He had moderate fatty and fried food intolerance. His appetite was poor with a gradual weight loss of almost 30 pounds in the past 5 years. Bowels were normal.

System review was non-contributory.

On examination the patient was a cachectic looking elderly white male. TPR was normal. B. P. 225/135. The lower edge of the liver was about 3 fingers below the costal margin. No further positive findings were found.

Laboratory work was non-contributory. Liver function tests were normal. There was no anemia. Sedimentation rate was 1mm/hour. Free hydrochloric acid was found on gastric analysis.

Cholecystography was performed on Sept. 27, 1949, with the administration of a refill. The gall bladder was normal, but gastric residue of priodax was noted. A gastro-intestinal series was recommended, and was performed on Oct. 18, 1949. A



Figs. 2a, b. Case III. J. W., revealing gastric residue of priodax, later shown to be secondary to a benign ulcer of pars media, verified at operation.

Fig. 3. Case IV. P. K., admitted a suspected coronary with no gastro-intestinal symptoms. Cholecystography revealed slight residue of priodax in the stomach, flaky in appearance and not well reproduced. On subsequent gastric examination there was a malignant neoplasm of the stomach, verified at operation. In spite of non-visualization the gallbladder was normal.

gastric ulcer was found on the lesser curvature of pars media. The patient came to operation on Nov. 1, 1949. A benign chronic ulcer of pars media was found, and a partial resection performed.

Case 4 (fig. 3) P. K., a 63 year old white male, admitted to the hospital on 7/12/48 with a chief complaint of chest pain of 5 weeks duration.

A previous attack of squeezing precordial pain with radiation down the left arm occurred 3½ years ago and lasted 24 hours. He was considered to have had a posterior myocardial infarct. Five days after the attack, EKG showed inverted T & Q waves and an elevated ST segment in lead III. An EKG 3 weeks later showed an iso-electric ST and no change in T or Q. A year later (3/11/47) T wave was normal, with a residual Q.

The patient had no further attacks until 5 weeks before admission when he again developed a squeezing precordial pain radiating down the left arm, associated with activity, and lasting 1-2 hours during attacks. He also complained of insomnia, asthenia, and a 12 pound weight loss.

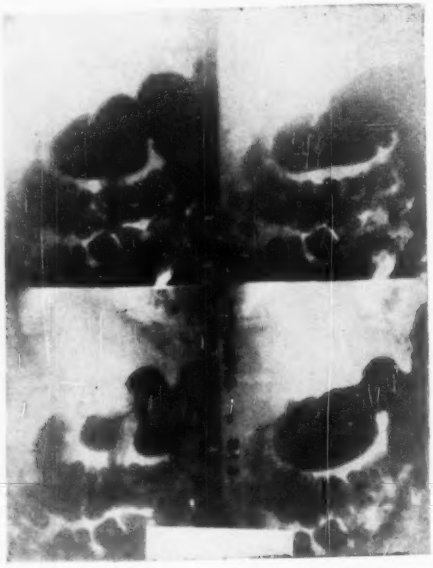
An EKG, taken on the outside before admission (6/15/49) showed a flattening of T3 and a somewhat low amplitude in CF V and VI. This was considered compatible with myocardial ischemia, but not infarction. On this basis, he was admitted to the hospital.

There were no gastro-intestinal symptoms whatsoever.

Physical examination revealed a 63 year old man, appearing chronically ill. The examination on the whole was essentially negative. T 99.2 P84 R20 Bp 120/70 Hb 11.1gm. RBC 3,290,000 WBC 15,300. Sedimentation rate 65. He was given routine coronary care and workup.

Repeated electrocardiographs revealed a normal pattern, with no changes.

Although the patient had no gastro-intestinal symptoms, a cholecystographic examination was ordered to determine whether a silent pathological gall bladder be an irritant reflex focus. The cholecystographic examination was conducted on two consecutive days, with the administration of a refill. The gall bladder was not visualized, but there was slight residue of priodax in the stomach. A gastro-intestinal series was therefore advised. This revealed a malignant infiltration of the greater portion of the body of the stomach.



Figs. 4a, b. Case V. F. W., admitted in 1945 with a history, considered clinically to be typical of gall bladder disease, and apparently confirmed radiologically by non-visualization. The significance of residue of gall bladder dye was overlooked. At operation a perforated duodenal ulcer was found, with only secondary inflammatory changes in the gall bladder.

Further investigation then revealed no free acid in the stomach.

Approximately two weeks after admission, the patient developed a continuous low-grade fever, for which no reason was found, and therefore assumed to be secondary to the malignant infiltration of the stomach.

The patient was operated upon on 8/15/49 when "a large nodular mass involving most of the body of the stomach" was found, "attached to the pancreas posteriorly." There was also a single metastatic nodule on the undersurface of the right lobe of the liver. The gall bladder was normal.

Comment: This case illustrated the significance of gastric residue of priodax during cholecystography. The patient was admitted as a coronary, with no gastro-intestinal complaints. Without a realization of the importance of this sign, the logical conclusion would have been a pathological gall bladder, which was disproven at operation. It is therefore equally important to appreciate that non-visualization of a gall bladder, even after the administration of a refill on the second day, does not represent biliary disease in the face of gastric retention of priodax.

During our periodic review of past films, the following case was encountered, which aptly illustrates the purpose of this communication.

Case 5 (fig. 4) F. W., a 54 year old white female was admitted to the hospital with a complaint of upper abdominal pain and vomiting of 6 months duration. She had had gaseous eructations, fatty food intolerance and constipation for years. The first attack recurred in 1937, and she was admitted to another hospital. Cholecystography and gastro-intestinal series were reported as negative.

The present episode began in May 1943, with right upper quadrant pain, radiating to the back, and accompanied by nausea and vomiting. There was no jaundice. During the past 6 months the patient lost 30 pounds.

On physical examination right upper quadrant spasm and tenderness were elicited. The remainder of the clinical work-up was non-contributory.

Cholecystography was performed on Nov. 27, 1943. The gall bladder was not visualized, and a diagnosis of a pathological gall bladder was made. In our present review of films gastric residue was noted. The importance of this finding was not appreciated. No gastro-intestinal series was recommended.

The patient was operated upon two days later. The surgeon's note follows in part. "There was a mass arising from the first portion of the duodenum, extending backward into the head of the pancreas." This was due to a perforated duodenal ulcer with a large inflammatory mass. "It produced 85% obstruction. The duodenum was markedly edematous and the gall bladder showed secondary inflammatory signs." An anterior gastro-enterostomy was performed.

A gastro-intestinal series performed a year later shows the duodenal ulcer and a well functioning gastro-enterostomy.

Two additional cases were encountered during the past two years, which revealed gastric retention during cholecystography, but with no demonstrable organic lesion on gastro-intestinal investigation.

Case 6 — N. P., a 15 year old white female was followed in the gall bladder clinic, with a complaint of recurrent attacks of epigastric and right upper quadrant pain, radiating to the back to the scapula. This had been present for several years, the attacks lasting hours or days. There was occasional nausea and vomiting. There was never any fever, nor any jaundice. Cholecystography on the outside showed non-visualization.

Physical examination was essentially negative. Laboratory work-up was negative. Bile was found on duodenal drainage, yielding a sterile culture.

Cholecystographic examination, performed on 4/30/47, failed to reveal any visualization of the gall bladder. On the other hand, however, there was evidence of gastric residue of priodax at the pyloric end of the stomach. A gastro-intestinal examination was performed revealing no organic lesion. There was, however, a functional disturbance with persistent antral spasm with a streak of gastric residue at the end of 6 hours.

The patient was operated on July 15, 1947 at another institution, where the gall bladder was found to be packed with stones.

Case 7 — V. B., a 33 year old female, had 4 admissions in one year for primary metrorrhagia. A D & C had been performed on Jan. 14, 1948.

In June 1949, she developed intermittent right upper quadrant pain, which was considered to be due to biliary dyskinesia. Cholecystography on the outside was reported to have resulted in non-visualization.

She was admitted for the fourth time on 7/7/49 with intermittent vaginal bleeding for the past 8 weeks. She had an enlarged uterus approximately the size of 8 weeks gestation. The A-Z test was strongly positive. The white count was 17,000. She was therefore operated upon 7/10/49. A left salpingo-oophorectomy was performed for ectopic pregnancy. At operation, the surgeon explored the right upper quadrant, and found a normal sized soft gall bladder." He found no evidence of calculi.

Eight days post-operatively, a repeat cholecystographic examination was performed, again with non-visualization of the gall bladder. Gastric retention of priodax was observed, and a gastro-intestinal examination was requested. This was not performed until a few months later. No abnormality was observed. There was no gastric residue.

Comment: The reason for the gastric retention of priodax in the latter two cases is not clear. The antral spasm may be a factor in case 6; and the fact that case 7 was post-operative, confined entirely to bed, may perhaps be the explanation in this instance.

The latter case also illustrates that in spite of non-visualization of the gall bladder on two separate occasions, the surgeon was not able to demonstrate organic gall bladder disease.

SUMMARY

1. Seven cases are presented, all of which were initially suspected of gall bladder disease. Gastric residue during cholecystography in each case was an important sign to investigate the gastro-intestinal tract as the possible site of the underlying organic lesion. Five cases out of a total of seven revealed organic lesions in the stomach or duodenum. The lesions need not necessarily be in an obstructive location, as is illustrated by the case of the lesser curvature ulcer in pars media, as well as the case of gastric neoplasm, involving mainly pars media.

2. Gastric residue during cholecystography represents a residue of at least 14 hours duration. As such, the residue is highly significant as an index of altered motility. Therefore, the likelihood of finding a gastric or duodenal lesion (not necessarily obstructive) is much greater than in those cases with a six hour gastric residue during the usual gastro-intestinal series with barium sulfate.

3. Pitfalls nevertheless do exist, even in those cases where the patients follow the instructions scrupulously. Being primarily a sign of altered gastric motility, anything that disturbs the physiological emptying time of the stomach may exhibit delayed gastric residue during cholecystography. At times this is easily explained as due to reflex spasm (from cholelithiasis in case VI). At other times it is more difficult to explain as in case VII when gastric residue was noted during cholecystography 8 days post-operatively. The fact that a gastro-intestinal series a few months later showed no gastric residue at 6 hours suggests a temporarily disturbed physiology in a post-operative patient confined to bed.

4. Non-visualization of the gall bladder is not synonymous with a pathological gall bladder, especially in the presence of delayed gastric evacuation of priodax, which is insoluble in the acid gastric juice. This point is well illustrated by the three cases (IV-V-VII) which showed non-visualization, and at operation no intrinsic gall bladder pathology was found.

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FAT DISTRIBUTION IN THE HUMAN LIVER AS REVEALED BY FLUORESCENCE MICROSCOPY

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THE morphologic distribution of fat in the liver has interested pathologists and physiologists for many years as this material is one of the few basic substances which can be identified by simple histologic methods. Since the metabolism of fat in the liver is still the subject of much conjecture, the interpretation of the histologic findings has varied throughout the years.

Recently the fluorescent microscopic demonstration of neutral fat by means of an aqueous solution of Phosphine 3R (1,2) has been described. A study of the fat distribution in the liver under various pathologic conditions by using this simple staining method is herein presented.

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MATERIAL AND METHOD

Of 372 livers observed at autopsy of patients suffering from various diseases including 24 cases of acute traumatic death, blocks were fixed in a 10% solution of formalin for at least two hours and not more than 16 hours. Frozen sections, and paraffin sections stained with hematoxylin-eosin were prepared. One frozen section of each case was mounted in tap water without staining and examined under the fluorescent microscope for Vitamin A fluorescence. The latter has a green hue and fades quickly. A second section, stained in 1% aqueous solution of Phosphine 3R for one minute, was mounted in glycerol-gelatin. The latter preparations are stable for three days. With this stain and with the filter system used, neutral fat exhibits a bright silver-white fluorescence against a dull yellow-brown background. This fluorescence, specific for neutral fats, distinctly demonstrates even very fine droplets. The fluorescence gradually diminishes under the ultraviolet light and does not reappear. The gradual fading is the cause of the limited stability of the preparation. Since the staining is performed in aqueous solution, the removal of fat droplets by the alcoholic solvents of the dyes used routinely, for instance, the scarlet red series, is avoided. The method for fluorescence microscopy was previously described (11).

TABLE I

ESTIMATION OF AMOUNT OF FAT IN THE LIVER FOUND IN VARIOUS DISEASES

Disease	No. of Cases	Kupffer Cells	Liver Cells	Total
Laennec's cirrhosis	35	+ to + +	+ + + to + + + +	+ + + to + + + +
Toxic cirrhosis	22	+ + to + + +	+ + to + + +	+ + to + + +
Toxic hepatitis	21	+ + to + + +	+ + to + + +	+ + to + + +
Biliary hepatitis	8	+ +	+	+
Infectious hepatitis	4	±	±	±
Fatty livers	7	+ to	+ + + to	+ + + to + + + +
Anemias (all types)	16	+ + + to + + +	+ to + + +	+ + to + + + +
Cardiovascular diseases	30	+ + to + + +	+ + + to + + +	+ + to + + +
Toxemias	25	+ + to + + +	+ to + + +	+ + to + + +
Malignant Tumors	45	+ + to + + +	+ to +	+ + to + + +
Diabetes	6	+ + to + + +	+ to	+ + to + + +
Nutritional deficiencies	6	+ + to + + +	+ to	+ + to + + +
Pneumonia, lobar	15	+ + to + + +	+ + to + + +	+ + to + + +
Pulmonary TB	11	+ + to + + +	+ + to + + +	+ + to + + +
Renal diseases	22	+ +	+ +	+ +
Brain tumors	6	+ +	+ +	+ +
Cerebral hemorrhages	9	+ to	+ to	+ to + +
Brain Abscess	2	+ +	+ +	+ +
Acute purulent meningitis	6	+ + to + + +	+ + to + + +	+ + to + + +
TB meningitis	5	+ + to + + +	+ + to + + +	+ + to + + +
Miscellaneous diseases (Periarteritis nodosa, Mycosis fungoides, Acute pancreatitis, Mesenteric thrombosis, etc.	15	+ + to + + +	+ + to + + +	+ + to + + +
Infants under 3 months	18	+ +	+ to	+ to
Children over 3 months	15	+ +	+ + to + +	+ to + +
Sudden accidental death	24			
TOTAL	372			

Results

Amount of Fat: The total estimated amount of fat fluorescence was graded from plus minus to four plus considering as one plus the amount of fat found in the livers of animals on well-balanced diets or of healthy individuals dying of sudden traumatic death (Table 1). In most pathologic conditions an increase of fat was found. For example, cardiovascular diseases, toxemias and nutritional deficiencies revealed as a rule higher amounts. The increased fat in many of these conditions may possibly be explained on a nutritional basis. Only in infectious in contrast to toxic hepatitis was the fat content lower than normal. In biliary hepatitis due to extrahepatic biliary obstruction the picture simulated in general the toxic form. Livers of Laennec's cirrhosis with and without jaundice had usually a very high fat content, independent of the degree of icterus present. The toxic form of cirrhosis also showed an increase, but in general, to a lower degree than the Laennec type.

TABLE II

DISTRIBUTION OF FAT IN THE LIVER LOBULES IN VARIOUS DISEASES

Distribution	*Diseases*
Focal with no pattern	Sudden accidental death
	Infectious hepatitis
	Toxic cirrhosis
	Renal cases
	Brain diseases
Peripheral	Toxemias
Central	Anemias (all types)
	Chronic pulmonary diseases
	Nutritional deficiencies
Diffuse	Laennec's cirrhosis
	Malignant tumors
	Toxic hepatitis (fatty type)
Intermediary	Passive congestion
	Toxic hepatitis (central necrosis type)

In infants dying at the ages of from one week to three months, there was a slightly higher fat content than in adults dying from traumatic death. In children between three months and three years the fat content approached that found in adults.

Distribution of Fat in Relation to the Liver Lobules: The fat distribution with self-defined lobular topography was found in several pathologic conditions (Table 2). Central distribution was primarily noted in anemias and in conditions in which anemia may have been prominent, such as chronic pneumonia, or pulmonary tuberculosis. The predominant central distribution in nutritional deficiencies was in this material probably conditioned by the associated anemia. Distribution of fat in the midzone of the liver lobules was observed in chronic passive congestion and in central necrosis of the liver in cases of toxic hepatitis. There it was accumulated in the preserved cells of the intermediary zone which surrounded the necrotic tissue of the centrolobular areas. The diffuse fat distribution predominated as expected in Laennec's cirrhosis and the fatty form of toxic hepatitis, as well as in diabetes, enterocolitis and various types of malignant tumors. Peripheral predominance of fat was chiefly found in diseases in which the effect of toxic substances was to be assumed (uremias, pregnancies and septicemias) without the liver being the primary target. The focal or spotty distribution characterized by irregular localization without pattern occurred in a variety of diseases as well as in cases of sudden accidental death, in infectious hepatitis and toxic cirrhosis.

Distribution of Fat Within the Liver Cells: The distribution of fat droplets within the liver cells showed no uniform picture. A perivascular arrangement of the droplets, that is, a distribution at the edge of the liver cells adjacent to the sinusoids, was usually found in children under three months and in healthy individuals dying of accidental death. Small fat droplets, irregularly and diffusely distributed throughout the liver cells were found in small amounts in infectious hepatitis and in large amounts in most cases dying from malignant tumors. Medium-sized to large fat droplets occupying a part or the entire liver cell were found mainly in chronic infectious diseases such as chronic tuberculosis, chronic enteritis or in anemia or chronic passive congestion. However, either the large fat droplets were usually intermingled with smaller droplets in the same cell or the fat showed no uniformity in the cells within the liver lobule inasmuch as the size of fat droplets in adjacent liver cells varied. The largest fat droplets were, as expected, found in grossly fatty livers and in cases of fatty cirrhosis. Fat seems to appear in the liver cells first in the areas surrounding the sinusoids. (Fig. 1). With the increase of the amount of fat, confluence of the smaller fat droplets occurs until the large fat drops fill most of or the entire liver cell. (Fig. 2).

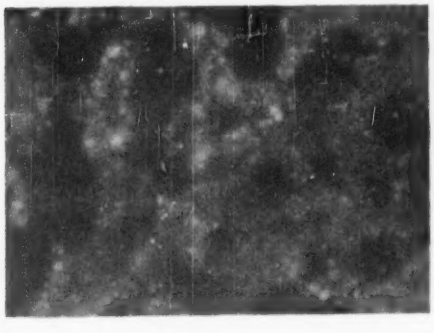

Fig. 1. Low power view. Small fat droplets located at the periphery of the liver cells.

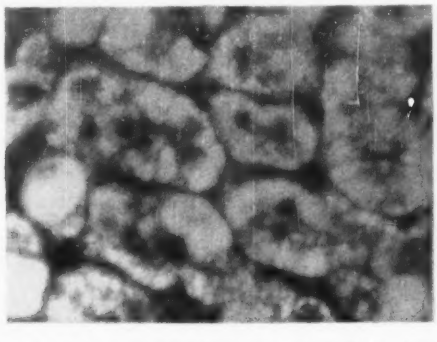

Fig. 2 High power view. Confluence of small fat droplets at the periphery of liver cells to form larger drops.

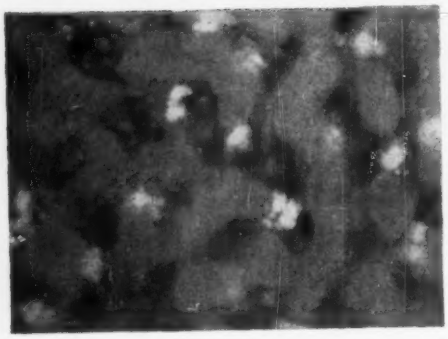

Fig. 3 High power view. Large fat droplets in the Kupffer cells in a diabetic patient. The liver cells contain but occasional small fat droplets.

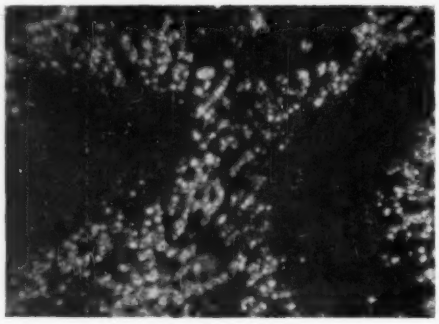

Fig. 4. Low power view. Fat distribution in the liver of a case of toxic hepatitis. The necrotic areas are almost free of fat.

Fat in Kupffer Cells: Fat was always observed in Kupffer cells, regardless of the cause of death, accidental or by disease. There was no characterictic pattern of fat distribution within the Kupffer cells in various pathological conditions. The Kupffer cells contained fat in spotty distribution, usually in those areas where the surrounding liver cells were fat-containing. In five out of six cases of diabetes, however, large fat droplets in the Kupffer cells were seen in diffuse distribution throughout the liver lobule. (Fig. 3). Another exception were the livers of patients who died of various forms of malignant tumors. In 32 out of 45 such instances, the Kupffer cells with small fat droplets were seen to be diffusely distributed throughout the liver lobule while only the liver cells in the vicinity of the central vein or of the portal fields were fat containing.

Relation of the Amount of Fat Found in Liver and Kupffer Cells: The amount of fat in the Kupffer cells was usually similar to that in the liver cells as observed in most pathologic conditions as well as in persons dying from sudden traumatic death. (Table I). However, there were some exceptions. In Laennec's cirrhosis, particularly the fatty variety as well as in fatty livers the Kupffer cells contained small amounts of fat as compared to the liver cells. A peculiar discrepancy of

TABLE III

FAT IN THE PORTAL FIELDS

Diseases	*Present in No. of Cases*	*Total No. of Cases Examined*
Laennec's cirrhosis (with and without jaundice)	6	35
Toxic hepatitis	1	24
Fatty livers	2	7
Passive congestion	2	30

the distribution of fat between Kupffer and liver cells was found in severe cases of toxic hepatitis, although the total estimated amount was about the same in both. Here, large numbers of fat droplets were found in the liver cells adjacent to the necrotic foci, while in the preserved areas bridging the necroses mainly the Kupffer cells contained small fat droplets in diffuse distribution throughout the lobule. (Fig. 4).

Fat in the Portal Fields: As a rule no fat was found in the portal fields. Occasionally, however, it could be observed in chronic passive congestion, fatty livers and toxic hepatitis. (Table 3). It occurred in the fibrous trabeculae separating the pseudolobules in Laennec's cirrhosis. The fat was seen in the form of small droplets occasionally taken up by phagocytes and usually in small amounts.

Lipofuscin: Lipofuscin, in the form of small granules showing brown-red fluorescence in unstained sections was found in all brown atrophic livers and in about one half of all cases of toxic hepatitis. It was further seen in about one third of cirrhoses of Laennec and of toxic type, as well as occasionally in livers in passive congestion, pernicious anemia, primary or metastatic tumors, biliary cirrhosis, infectious hepatitis and eclampsia. It was even seen in livers of patients dying of sudden accidental death. It was located at the edge of the liver cells in the areas surrounding the bile capillaries and only if present in abundance was it seen more diffusely distributed through the liver cells. The granules were usually present around the center of the lobules, and only in the presence of a large amount, did they spread toward the periphery. Frequently, but not always, they showed a silver-white fluorescence after staining with Phosphine 3R. However, there was a somewhat duller sheen as compared to the fluorescence of the lipids.

DISCUSSION

The importance of the liver in the metabolism of lipids has been recognized for a long time. It is generally agreed that it plays an important part in the normal utilization of fat in the body. The accumulation of fat in the liver under pathological conditions such as infectious processes, toxemias in pregnancy and following poisoning with chloroform, phosphorus or benzol may be the result of two mechanisms: Firstly, an excess of fat may be set free from the adipose tissue and may accumulate in the liver; secondly, normal amounts of fat reaching the liver may accumulate there owing to the inability of the damaged liver cells to metabolize it. However, as observed previously, the accumulation of fat does not necessarily go hand in hand with evidence of liver cell damage, as noted in viral hepatitis in which despite marked functional and anatomical damage of the liver cells the amount of fat in the liver is normal or decreased.

In a recent report of the systematic attempt to correlate the fat distribution of the liver with the functional status of the organ and the pathological conditions of the patient, Sachs (3) came to conclusions essentially in agreement with ours. The deposition of fat in the center of the liver lobule as seen in anemia and anoxemia (4,5) or following administration of certain poisons such as carbon tetrachloride (6,7) and chloroform (8,9) has been observed before. In general, the peripheral predominance of fat distribution was chiefly found in diseases—uremia, septicemia, toxemia in pregnancy—in which the liver was not the primary target of the toxin and where the peripheral cells of the liver lobules adjacent to the arterial blood supply are the first to be injured. The large amount of fat found in the cases of Laennec's and particularly fatty cirrhosis is in conformity with other studies in which specific deficiency factors favoring the accumulation of fat are discussed (10,11,12,13).

The livers examined by us were never free of fat, neither in children nor in apparently healthy individuals, as noted before (14,15). Our investigation suggests that the fat appears first on the edge of the liver cells adjoining the sinusoids and spreads from there into the other areas of the cells, until the cytoplasm is diffusely studded with small fat droplets or until by confluence of several small droplets the characteristic large fat drop forms.

The presence of fat in small amounts in the Kupffer cells in normal individuals (16) and the discrepancy between the distribution of fat in Kupffer and liver cells in cases of diabetes (17) has been discussed by others. In our series the distribution of the lipid containing Kupffer cells corresponded well with that of the fatty parenchymal cells. The only unexplained exception in addition to the findings in diabetic patients were the livers of patients dying of various malignant tumors, in a large number of which Kupffer cells containing much fat were seen diffusely distributed throughout the liver lobule, while the liver cells revealed fat only in the vicinity of the central veins or of the portal fields.

There were occasionally small fat droplets observed in the portal fields, either free or in phagocytes. It was noted mainly in cases of Laennec's cirrhosis in which large fat droplets had accumulated at the periphery of the pseudolobules.

Lipofuscin (18) was frequently noted, particularly in brown atrophic and cirrhotic livers as well as in toxic hepatitis. It reacts with various fat stains (19). However, it stains irregularly and with a somewhat different shade than the lipids. Frequently, the granules located most centrally did not stain with Phosphine 3R, while those at the periphery did. Other investigators have already claimed that lipofuscin in aging state does not give fat reaction (20,21). Therefore lipofuscin in the center, being the oldest, does not give fat stain while the younger granules at the periphery are lipid-containing. A grouping of fat droplets, without lipofuscin, around the bile capillaries was not observed. Possibly, the peribiliary arrangement of fat as described by others is due to lipid-containing lipofuscin granules.

The fluorescence microscopic examination of frozen sections stained with Phosphine 3R appears valuable to investigate the distribution of fat in the liver. The method is simple; it distinctly visualizes even very fine droplets and since the staining is performed in aqueous solution more of the fat droplets are stained than with alcohol-soluble dyes.

SUMMARY

The fat distribution in the human liver was reinvestigated using fluorescent microscopic examination of frozen sections stained with Phosphine 3R. There was an increase of fat in most pathologic conditions, except in infectious hepatitis in which the fat content was lower than normal. There was a considerably larger amount of fat in the parenchymal cells as compared to the Kupffer cells in fatty and cirrhotic livers. On the other hand, the amount of fat in the Kupffer cells was increased in diabetics and in most patients dying of various malignant tumors. Fat was also noted in the fibrous trabeculae in Laennec's cirrhosis. The development of fatty metamorphosis from small to large fat droplets in the liver cells was followed up.

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DIABETES MELLITUS AND PERNICIOUS ANEMIA

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FORMERLY, it was accepted that the coincidence of diabetes mellitus and pernicious anemia was to be found extremely seldom. Naegeli (3), Adams (1), Goudsmit (2) Bowen and Aaron (4) and Olivier (5). Although the relative frequency of the two diseases has been stated by statistics, only a few cases of the combination had been observed. Adams found among 2000 cases of diabetes and 1000 of pernicious anemia but three combined cases; Goudsmit among 1650 cases of diabetes and 379 of pernicious anemia, only 5. Others found the combination between 0.36 to 2 per cent of the diabetic cases, Beckert (6) 1 per cent, Watson (7) 1.05 per cent, Murphy and Howard (8) .2 per cent, Murphy and Maxon (9) 0.36 per cent. Murphy and Howard (8) saw among 440 cases of pernicious anemia 9 which developed diabetes; Wilkinson (10) saw in a series of 10,038 cases of diabetes 18 with pernicious anemia, and among 2461 cases of pernicious anemia 15 with diabetes.

But recently Root (11,12,13) has collected a total of 140 cases of the combination, among them 65 alone observed by him in one hospital (Deaconess Hospital) in Boston. From this report we must conclude that the association of the two diseases is much more frequent than has been believed.

Root is of the opinion that this increased frequency is due to a longer duration of life which is the result of progress in therapy of the diseases (insulin, liver); also we must not forget the greater effort made to insure an earlier diagnosis.

In the opinion of many observers, the combination occurs only by chance and no causal connection between both diseases can be found, Shookhoff (18), Goudsmit (2), Benjamin (14), Hitzrot (15), Kaufmann and Thiessen (16), Schulten (17).

But certain signs and symptoms defy this opinion and compel us to consider a relation between diabetes and pernicious anemia. Root mentions that numbness and tingling in the hands, feet and legs are common *symptoms* in both diseases, to which can be added atrophic tongue and diarrhea.

When we look for other *signs* common to both diseases there is one sign which is of greatest interest: Achylia gastrica. We know achylia gastrica to be present in pernicious anemia in 100 per cent (the reason for my suggestion that we call the disease "macrocytic achylic anemia") (19); it is found in diabetes in an amazingly high percentage. The number fluctuates between 19 and 33 per cent. Root (13), who collected the cases found among 300 diabetic patients 131 with complete anacidity=52.8 per cent. Others believe that achlorhydria even occurs in more than 40 per cent of all patients with diabetes. Rabinowitch and co-workers (20) in 30 percent*; Moore (22) in 39.7 per cent; Katsch (23) found among 10 patients with diabetes 7 with achylia gastrica=70 per cent.

It is believed that diabetes produces a gastritis which leads to achlorhydria. In Klein's (24) opinion, hastiness and greediness of a non-treated patient must lead in due time to gastric catarrh and achlorhydria. Others believe that the cause of achlorhydria is not uniform: There can be gastric and cholecystic disturbances, changes in the chlor-metabolism, and certainly constitutional causes.

But the development of gastritis cannot be caused by diabetes, since in many cases pernicious anemia precedes diabetes. Root (13) saw among 79 cases diabetes first in development in 56, and pernicious anemia first in 11; Murphy and Howard (8) in 9 patients, McGregor (25), Wilkinson (27) in 6 cases, Benjamin (14) and others.

The important question is what do we find in diabetes: Achlorhydria or achylia gastrica?

One might be inclined to consider this question useless because, in general, achlorhydria and achylia gastrica are used synonymously. But they are quite different: Achlorhydria is merely lack of free hydrochloric acid, a symptom found in many conditions; while achylia gastrica is an entity showing three strictly circumscribed signs: 1) Absolute lack of gastric juice; 2) Disturbance of motility; 3) Disturbance of chymification.

For positive diagnosis of achylia gastrica, the alcohol-histamine test is not sufficient; the Boas-Ewald test meal must be used.

Since achylia gastrica is the only term which precisely defines this condition, it is to be assumed that authors who write "complete anacidity" mean achylia gastrica. Therefore, inasmuch as we have achylia gastrica constitutionalis and not achlorhydria in pernicious anemia, the same must be true of combined cases of diabetes and pernicious anemia. In the few cases of diabetes I have examined, I have found typical achylia gastrica. In the future, attention of examining physicians must be called to the difference between achylia gastrica and achlorhydria.

Thus the *connecting link* between diabetes and pernicious anemia is achylia gastrica; it is the fundamental factor in the association of the two diseases, Root (13), Eminson (26), Wilkinson (27). Only in the cases of diabetes with achylia gastrica can pernicious anemia develop.

The second important element in both diseases is *heredity*.

Today, it is the prevailing conception that the primary cause of diabetes is a congenital biological inferiority of the islands of Langerhans in the pancreas with disturbance in insulin production or secretion; a minus-variant hereditary in the constitutional dispostion, Naunyn (28), Umber (29), Joslin (30), Fitz (31). Naunyn who first stressed its importance found heredity in 18 per cent of his cases, Joslin, among 6357 cases, in 24.5 per cent; Umber (29) and co-workers, Seckel (32) and Finke (33), in 25.5 per cent; van Noorden and Isaac (34) in 25.4 per cent, Weichselbaum (35) in 25 per cent.

P. White and G. Pincus (36,37), give four facts in favor of the theory that the potentiality for developing diabetes is inherited:

*In a later publication Rabinowitch (21) saw 44 per cent.

First factor: The almost simultaneous occurrence of diabetes in both members of similar twins.

Second factor: The greater incidence of diabetes in the blood relatives of diabetics than in those of a control population.

Third factor: The demonstration of Mendelian ratios.

Fourth factor: The demonstration of expected ratios for diabetes in presumably latent cases.

In a comprehensive paper on achylia gastrica I (19) have shown that we have the same factors present in achylia gastrica.

Achylia gastrica too is a minus-variant; the glandular cells of the stomach develop histologically apparently normally, but they function poorly or not at all. It is an inherent condition, constitutional in its character.

Let me give you a brief resume of the similar existence of these factors in both diseases. (The full exposition for diabetes can be found in the papers of White and Pincus; for achylia gastrica in my paper).

First factor: P. White and G. Pincus (36), in a series of 96 pairs of twins, had 33 pairs of similar, 63 pair of dissimilar twins. Among the 33 pairs of similar twins, in at least 16 pairs both were diabetics, i. e. 48.5 per cent; whereas in only two (3.2) per cent of the 63 pairs of dissimilar twins did each twin have the disease.

Then H. Berg (38) showed like results in a series of 133 pairs of twins with diabetes. Of these, 46 pairs were similar, 87 dissimilar; in 65 per cent of the 46 pairs, both twins had contracted diabetes; of the dissimilar twins, only 22 per cent.

Umber (29) found among 19 pairs of similar twins 15 with diabetes=84 per cent.

The occurrence of pernicious anemia in similar twins is described in 7 pairs. 4 pairs had achylia gastrica with pernicious anemia; in the other 3 pairs one twin had pernicious anemia and the other achylia gastrica developing into pernicious anemia.

There is one pair of similar twins in the literature where both have diabetes and pernicious anemia, Kaufmann and Thiessen (16).

WOMEN, 55 YEARS OF AGE

One sister had pernicious anemia, diabetes and hyperthyroidism. The twin sister developed diabetes some years later than her sister. She had achylia gastrica and hyperthyroidism. At this time her blood examination showed hemoglobin 88, erythrocytes 4 020,000, leukocytes 5600 with 48 per cent lymphocytes. Color index 1.09. Average erythrocyte diameter 8.24 μ. Without doubt, this is an early stage of pernicious anemia.

Second factor: For both diseases, diabetes and pernicious anemia, incidence in blood relatives is demonstrated.

Pincus and White (37) found the total incidence of diabetes in blood relatives 6.7 per cent, compared with 1.23 per cent in the control non-diabetic population; Umber in 26 per cent in contrast to 2.8 per cent in a control population; Wilkerson and Krall (39) found a family history of diabetes in 38.6 per cent of the diabetic and in 18.2 per cent in the non-diabetic persons. I. Moellerstroem (40) saw in his material consisting of 1220 families with 5932 children, diabetes in 1449=24.4 per cent. Among 30 children, both of whose parents were diabetic, 14=46.7 per cent had the disease. Joslin and co-workers (30) saw diabetes among parents and grandparents in at least twice the expectation in a random sample.

The familial occurrence of achylia gastrica in relatives of patients with pernicious anemia is on the average about 20 per cent. Askey (41), Werner (42), Kaufmann and Thiessen (16) found achylia gastrica in relatives of pernicious anemia patients to be twice as high in *near* relatives as in *distant* ones (Werner: 19 per cent to 9 per cent).

The mutual heredity is shown by Root (13): In 13 per cent of the cases with combined pernicious anemia and diabetes, anemia was known to exist in the family, and diabetes in 33.3 per cent of these families. One of Goudsmit's (2) patients with the combined diseases had a brother and a sister with diabetes. Outstanding is the case of George R. Minot (43), in whose ancestry both diseases were frequently encountered.

My own case: Male, 34 years of age, with diabetes. Anamnesis showed that his mother died of pernicious anemia (with achylia gastrica). He complained only of diarrhea. Gastric examination: Typical achylia gastrica. Blood findings: Hemoglobin 97; erythrocytes 4.406,000; color index 1.1; leucocytes 5280. Polynuclear leucocytes 60 per cent; stab-leucocytes 2 per cent; transition cells 9 per cent; eosinophile leucocytes 3 per cent; lymphocytes 26 per cent; macrocytosis; slight polychromacy. Diagnosis: Diabetes mellitus, achylia gastrica with latent pernicious anemia.

There was no diabetes and no other case of pernicious anemia in the family as far as the patient knew.* A personal examination of members of the family was impossible because the patient came from Egypt. His mother had achylia gastrica and pernicious anemia. This led us to the gastric examination which brought to light his achylia gastrica and a blood-finding that allowed the diagnosis of latent pernicious anemia. These are the cases which must be carefully observed, as we know by experience that they can develop into pernicious anemia. This case corresponds to the case of potential diabetes which Wilkerson and Krall (39) mentioned.

Third factor: The type of Mendelian ratio has not yet been unconditionally demonstrated for both diseases. White and Pincus (36), Hanhart (44) and others believe that it is the simple recessive type; others believe in the dominant character in diabetes mellitus, Perkins (45).

In achylia gastrica most observers indicate the dominant type, Mustelin (46), Weitz (47), Werner (42), Kaufmann and Thiessen (16).

Fourth factor: The demonstration of expected ratios in presumably latent cases.

White and Pincus (36) refer to the significant high blood sugar findings in relatives of diabetics: Among 169 close blood relatives of diabetics, 14 per cent by routine, 25 per cent by tolerance test had had supranormal values compand with 2 per cent of 125 control individuals.

Another fact well known for a long time, to which Colwell (48) called attention is the so-called anticipation. This means that a hereditary disease in three generations of a single family appears from generation to generation at an earlier age. We find it in pernicious anemia too. In Mustelin's (46) case, pernicious

*Since the writing of this paper, the patient's sister has developed diabetes.

anemia appeared in the mother at 67, daughter at 42, grandchild at 24, all with typical achylia gastrica. We assume that, due to the congenital achylia gastrica, there is diminished storage of the antianemic principle in the liver, and that the exhaustion becomes effective at an earlier age in each successive generation.

The blood examinations in achylia gastrica show changes that allow us to make the diagnosis of latent pernicious anemia (49). We find especially macrocytosis, color index above 1, polychromacy, leucopenia with hypersegmentation of the polynuclear leucocytes, lymphocytosis, diminished monocytes and platelets. In a great number of such cases it is possible to observe the transition to pernicious anemia (50).

There is still another conformity in both diseases: *The pathological changes.*

In diabetes there is hyalinization, fibrosis, lymphocytic infiltration—degenerative and destructive lesions of the islands of Langerhans.

But there is a much more important fact that has puzzled the pathologists: In many cases the islands of Langerhans have been normal. Cecil (51) states that in 12 per cent of the examined cases no abnormalities have been found. Out of 484 pancreases studied carefully by Warren (52) among 527 autopsies, 127 or 26 per cent were absolutely normal histologically. Warren writes: "It is rather difficult to conceive how we can have an insular diabetes with normal islands of Langerhans."

We have the same condition in achylia gastrica and therefore in pernicious anemia. The pathological changes in achylia gastrica are fibrosis, cystic dilatation of the gastric glands, round-cell infiltration, progressive atrophy. The round-cell infiltration as a sign of gastritis has been highly overestimated.

Actually there is no gastritis at all in achylia gastrica and pernicious anemia, Weinberg (49). Today it is generally accepted that the gastric lesion present in pernicious anemia is quite different from gastritis. The pathological changes are to be found only in cardia and fundus, Weinberg (49), Meulengracht (53), Magnus and Ungley (54), Cox (55).

But the decisive, comparable point is that in achylia gastrica and pernicious anemia too there are cases with *no* pathological changes at all. In three out of eleven patients with achylia gastrica who died of pernicious anemia, and whose stomachs I examined microscopically, there were no changes of gland cells—only very slight round-cell infiltration (1918) (49), which today is considered a normal finding in adults, Guiss and Stewart (56), Magnus (57).

Ricker (58) and M. Brown (59) have described one case each of pernicious anemia wth entirely normal mucosa; Lubarsch (60), Einhorn (61), on the basis of examination of mucosal particles, described the same; Passey (62) also, from a fragment of gastric mucous membrane removed during an appendectomy on a patient with pernicious anemia.

The same phenomenon occurs in both diseases: Complete absence of secretion without any pathological changes. Functional disability of the cell may exist withouts any obvious anatomical alteration, MacCallum (63).

This insufficiency of the secretion with normal anatomy of the glands is due to a constitutional, inborn inferiority of the glands.

When there is a minus-variant of one organ, there is the possibility that the same condition is co-existent in another one. This is the case in diabetes when it is coupled with achylia gastrica.

What is known about a disturbed carbohydrate metabolism in achylia gastrica and pernicious anemia?

Hartfall (64) found among 336 cases of achylia gastrica three with diabetes. Watson (7) obtained in 6 patients with achylia gastrica sugar tolerance curves with an abnormal bloodsugar curve. Shay, Gershon-Cohen and Fels (65), in 48 per cent of the curves of individuals with achylia gastrica, saw impairment of sugar tolerance compared with 16 per cent of a control group.

In pernicious anemia we have more facts. In 16 patients with pernicious anemia, Johnson (66) found the fasting bloodsugar above normal. Meulengracht and Iverson (67) repeated the same test with the same result: An increase in bloodsugar levels and a delay in the return to normal. Rennie (68) saw in 19 patients with pernicious anemia definitely abnormal tolerance curves with the glucose tolerance test in 58 per cent (11 cases); 8 of these had prolonged curves, 3 abnormally high ones. Goudsmit (2) reported that in 5 out of 8 cases with pernicious anemia, the sugar tolerance test gave a rise of bloodsugar to over 0.17 per cent. Giffin and Bowler (69) showed in two of their anemia patients a disturbed sugar metabolism; Isaac and Handrick (70) found in their cases of pernicious anemia the bloodsugar level considerably higher than normal.

Knowledge of heredity in diabetes depends upon a more systematic examination of relatives of a diabetic patient. Of course the successful experiment in Oxford, Massachusetts, where 3516 of the town's population of 4983 underwent blood and urine examinations, by which 30 new cases could be added to the previously known 40, would be the most efficient method (39). But examination of the whole population will prove too ambitious an effort to be transferred into immediate reality. So we must, perforce, resign ourselves in practice to the still valuable and helpful examination of all the relatives, near and distant, of a patient with diabetes.

The same can be said of pernicious anemia. Martius (71) long ago proposed the gastric examination of all school children to detect achylia gastrica. A difficult undertaking certainly, and one never tried. But examination of relatives of patients with pernicious anemia has been undertaken, and it was in such cases that the diagnosis of latent and early pernicious anemia was made, (49, 50, 41).

Research in diabetes is much more advanced than in pernicious anemia. The scientific clinical investigation in pernicious anemia has not kept pace with interest in the therapy. We can take it for granted that, as in diabetes, there are numerous unrecognized cases of pernicious anemia. Everything that has been proposed and done in diabetes to discover these unrecognized cases can and should be applied to pernicious anemia.

The prospect for the prevention of pernicious anemia is, in my opinion, even greater than in diabetes, because it seems doubtful that premorbidity will be recognized by the tolerance test in persons liable to develop diabetes, Hanhart (44). Once the diagnosis of achylia gastrica is made, we know that this is a potential case of pernicious anemia and can give the proper therapy.

SUMMARY

We have shown that there are deep-rooted connections between diabetes mellitus and pernicious anemia; both are constitutional anomalies. Both have the same origin: Congenital biological inferiority of an organ. In diabetes it is the deficiency in the islands of Langerhans of the pancreas gland: Disturbance in insulin production or secretion. In pernicious anemia it is the deficiency in the corpus and fundus glands of the stomach (achylia gastrica): Disturbance in the intrinsic factor production or secretion, Fox and Castle (72). Furthermore, what Colwell (48) has said of diabetes, "Diabetes is inherited and begins at birth," is equally true of achylia gastrica; I would, however, prefer the term 'present at birth'.

In both diseases, in spite of the deficiency in the function, there can be a normal gland picture. Both disturbances can be combined, as is seen in diabetes with achylia gastrica in more than 40 per cent; and in achylia gastrica and pernicious anemia with disturbance of the carbohydrate metabolism. In such cases both diseases can develop. The knowledge of these connections is of importance to the practice.

In patients with diabetes, gastric analysis and blood examination should be added to the routine examination, especially in patients with achylia gastrica who should be considered potential cases of pernicious anemia. On the other hand, patients with pernicious anemia should be examined for signs of disturbed carbohydrate metabolism.

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CONCURRENT PATHOLOGY OCCURRING WITHIN AND WITHOUT THE GASTROINTESTINAL TRACT CAUSING GASTROINTESTINAL SYMPTOMS

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IT is common knowledge that pathology outside of the gastrointestinal tract may cause gastrointestinal symptoms. The purpose of this paper is to point out the frequency of concurrent pathology, that is, pathology outside of the gastrointestinal tract occurring simultaneously with pathology within the gastrointestinal tract, both causing gastrointestinal symptoms. The frequency of such concurrent pathology suggests that gastrointestinal investigation should be done more often, even though extrinsic pathology has been discovered which seems to explain all the gastrointestinal symptoms.

Innumerable articles have been written on the gastrointestinal manifestations of urologic disease, on the gastrointestinal symptoms in pulmonary tuberculosis, in coronary disease, in pelvic infection, in pernicious anemia, in brain tumors, etc. The conditions which may produce gastrointestinal symptoms may be classified largely into ten groups:

1st Group: *Intrinsic Gastrointestinal Pathology.* In this group I would place all the diseases of the stomach and intestines, such as ulcer, cancer, gastritis, polyp, regional enteritis, appendicitis, diverticulosis, etc. Under this head would also fall digestive upsets due to food indiscretion, poisons and other irritations caused by ingestion of foods, including overeating, too rapid eating etc.

2nd Group: *Pathology in Extrinsic organs which produces Gastrointestinal symptoms reflexly.* In this group fall such disorders as Nephrolithiasis, twisted ovarian cyst etc.

3rd Group: *Circulatory Disturbances.* "When a patient complains of his heart, think of his stomach, when he complains of his stomach, think of his heart." In latent cardiac decompensation with congestion of the liver and splanchnic area, the patient may complain of digestive discomfort long before it becomes manifest that decompensation has developed. In coronary disease the pathogenesis of the gastric manifestations is probably a combination of liver and gastrointestinal congestion and reflex disturbance through the vagus nerve. Aneurysm of the abdominal aorta or arteriosclerosis of the splanchnic vessels are other instances in which circulatory disorders may be the cause of digestive disturbances.

4th Group: *Toxemia.* In this group would fit gastrointestinal disturbances caused by nephritis, uremia and pregnancy.

5th Group: *Infectious Diseases.* The order in which these groups are enumerated would vary in probability depending on a number of factors. For instance, the patient's age. In a child with vague gastrointestinal complaints, the 5th group, that is, Infectious Diseases, would be the most probable etiology. Besides the acute infections and the exanthemata, in this group would be placed such chronic infections as syphilis and tuberculosis, diseased teeth, tonsils and sinuses.

In one of my patients, age six, I was able to demonstrate roentgenologically that in acute infection pylorospasm with retention may develop. In this case the child was examined for vague gastric complaints and arrangements were made to do a gastrointestinal series one week later. One week later without further examination and without taking the child's temperature, the child was given barium and the X-ray series started. The patient returned eight hours later and the X rays showed a retention of about one half of the barium. That night the child vomited and complained of severe gastric pain. An examination revealed a temperature of 104 and acute follicular tonsilitis. Two weeks later the gastrointestinal series was repeated and was perfectly normal without six hour retention.

One may speculate as to why acute infection may cause gastric symptoms and vomiting. A theoretical explanation would be that the liver in its detoxifying capacity secretes toxic material along with bile into the duodenum, thereby producing duodenal irritation re-

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sulting in pylorospasm, abdominal cramps and either constipation or diarrhea. With this idea in mind the old fashioned remedy of a cathartic and/or enema at the onset of infectious disorder seems quite rational.

6th Group: *Endocrine Gland Disorders.*

7th Group: *Blood Dyscrasias.* Pernicious Anemia and Leukemia often simulate gastric neoplasm.

8th Group: *Allergy.*

9th Group: *Neurosis and Psychoneurosis.*

10th Group: *Concurrent pathology*, consisting of Group 1 (intrinsic gastrointestinal pathology) occurring simultaneously with any of the other groups.

It is not my purpose in this paper to go into detail as to how each of these groups of disorders develops gastrointestinal symptoms, but rather to point out that the responsibility of recognition of pathology outside of the gastrointestinal tract as the etiology of gastrointestinal symptoms has been emphasized so as sometimes to overshadow the fact that the patient may have in addition to the known extragastric pathology, an intrinsic condition responsible for his symptoms. To illustrate this point, let me cite a few cases.

Case 1: S. M. Age 49, married, two children alive and well, came to my office 3/29/33. Chief complaint: Past six months she had indigestion, occasional diarrhea, had become dyspneic, nervous, and developed palpitation on slight exertion. During the past two months she had vomited on occasions and developed marked weakness. She had lost thirty-five pounds. Examination revealed an exophthalmic woman. Weight: 118, B. P. 130/70, a diffuse enlargement of the thyroid, coarse tremor, pulse: 120, Temp: 98. Lungs: negative. Heart: Slightly widened base and left ventricle. Abdomen: negative, except for tenderness in epigastrium and over a bounding abdominal aorta. B. M. R.: plus 50.

The diagnosis of thyrotoxicosis was evident. The gastrointestinal symptoms could be explained on the grounds of toxic goitre. *However a gastrointestinal X-Ray series showed advanced pyloric carcinoma.*

The patient was operated on at Bellevue Hospital April, 1933, and a thyroidectomy was successfully performed. Microscopic pathological examination of the thyroid specimen showed no evidence of metastases from the gastric carcinoma. In May, 1933, laparotomy was performed at Bellevue and gastric carcinoma with metastases to the liver was discovered. She died in July, 1933.

It is apparent that in the case of S. M. the definite establishment of the presence of a severe thyrotoxicosis seemed sufficient to explain her diarrhea, weakness, epigastric distress, vomiting, and the loss of thirty-five pounds in six months. However a further study revealed a concurrent intrinsic gastric condition.

Case 2: Y. G. age 52, married, five children, sent to me 11/18/33 with roentgenograms taken by a urologist revealing bilateral kidney calculi. Dr. H. M. Sternberg, who referred the patient, felt that there was concurrent intrinsic gastrointestinal disease. For several years she had been complaining of epigastric pains, radiating to the back, subscapular region and to the right upper quadrant. For four weeks prior to the time I saw her, she had been complaining that her pains had become worse, especially at night. Her appetite was poor and she had lost some weight. Nausea but no vomiting. There was no nocturia, dysuria or frequency. The remainder of the history was irrelevant.

Physical examination showed an asthenic type of woman. Pupils reacted. Weight: 114, B. P. 110/70. Heart: negative. Lungs: negative. Abdomen: Distended, slight tenderness in the right upper quadrant, no masses.

Laboratory data: Stools: Markedly positive for occult blood. Urine: Specific gravity 1015, occasional cast, trace of albumin. Gastric analysis: 50 free HCL; 70 total acid, markedly positive for occult blood.

G. I. X-Ray: Penetrating ulcer on posterior wall of duodenum, with barium remaining in the the niche of the ulcer at six and twenty-four hours. Some gastric retention after six hours but none after twenty-four hours.

Course of the case: Patient put to bed. Modified Sippy diet and alkaline powders. Daily gastric lavage for four days, then every second day for one week. January 29, 1934, all symptoms were gone and the patient weighed 117. February 22, 1934, weight 119. No complaints but was apprehensive about her kidneys. April 4, 1934, no complaints, weight 124. Patient was last seen June, 1948. She is now sixty-seven years old and has no gastrointestinal complaints.

In the case of Y. G. the patient had been advised to have an operation performed for the purpose of removal of the kidney calculi. Such an operation would have been fraught with danger especially if there were severe post-operative vomiting and retching, and hardly would have relieved the patient of her chief complaint. It is questionable whether operation even now is indicated inasmuch as the patient is symptom free, at any rate she is in far better condition to survive a radical procedure now than when there was a concurrent penetrating duodenal ulcer present.

Case 3: A. B.: Thirty-nine years old, single. Seen by me on 2/27/44. He began to complain four months before I saw him of epigastric distress *stat p.c.*, regurgitation, "rolling of intestines." Two months ago his physician had noted a right inguinal hernia and sent him to Bellevue Hospital where a herniotomy was done. Instead of relieving his gastric symptoms, he rapidly began to lose weight, thirty-eight pounds since onset and epigastric pains persisted.

Physical examination: Weight: 110, B.P. 110/80. Pupils reacted. Heart: negative. Lungs: negative. Abdomen: tender in epigastrium. Laboratory data: Wassermann: negative. Gastric extraction: No free HCL.; markedly positive for occult blood. Stools: Markedly positive for occult blood. G. I. X-Rays: Gastric carcinoma involving more than one half distal half of the stomach. Patient refused laparotomy. In May, 1944, he developed ascites and died July, 1944.

In the case of A. B. his gastric symptoms were apparently considered as due to his hernia. It has not been frequent in my experience that hernia causes any gastrointestinal symptoms unless there is some mechanical obstruction. *The presence of inguinal hernia, especially after forty, should put one on the alert for some increase in intra-abdominal pressure such as may be caused by gastrointestinal malignancy, retro-peritoneal sarcoma or hypertrophied prostate with straining at urination.*

Case 4: N. A., Married, one child, relative of a physician, was brought to me by the physician, 11/1/42. His past history was interesting. In 1925 he had a splenectomy for throm

Case No. 5. Fig. 1. Pyloric carcinoma. Large branched calculous rt. kidney.

bocytopenic purpura. He felt well until March, 1931 when he awoke one night with sudden pain in the left breast. An electrocardiogram was taken and proved to be negative. For three months thereafter he felt well during the day but would awaken at night with very severe pains in the upper abdomen. In June, 1941, he went to the Beth Moses Hospital of Brooklyn, New York and laparotomy revealed cholelithiasis. Cholecystectomy was performed and he felt better for one month. The attacks recommenced and his physician felt that a vacation would relieve him. He felt there was some psychic factor. The patient did feel much better while on his vacation but in January, 1942 the attacks again began. During the day the patient felt well, but at night there was severe pain in the right upper quadrant. At first this was relieved by hot milk, but in the last three weeks only one half grain of morphine gave any relief. There was only occasional vomiting. Appetite was good and patient did not lose weight. Nocturia three or four times but patient believed this was because he was awakened by pain. Various consultants had made suggestions such as hepatic or pancreatic stone. On physical examination the patient was cheerful, stocky build. Weight: 154, B. P. 100/80. Good hemic component. Infected tonsils. Heart: negative. Lungs: negative. My impression was that renal calculus should be ruled out. A urologist cystoscoped and X-Rayed the patient and no pathology was found. February 2, 1945, we fluoroscoped the patient and an ulcer of the duodenum was discovered. Sippy diet gave only slight relief. The patient subsequently went to the Mayo Clinic for corroboration of the diagnosis of ulcer, which was confirmed, and he was operated on at the Brooklyn Jewish Hospital. A stenosis of the second portion of the duodenum from cicatrization of a chronic ulcer was found. The attacks ceased after the operation and the patient has been well since.

In this case the knowledge of the presence of cholelithiasis obscured the real cause of the patient's symptoms which was a stenosing duodenal ulcer. It has been demonstrated time and again that peptic ulcer is not infrequently associated with gall bladder pathology and chronic appendicitis, so that an investigation which discloses gall bladder disease should not be considered complete unless concurrent gastrointestinal pathology has been ruled out.

Case 5: H. H., age 69, had been known by his family doctor to have a large calculus in his right kidney for many years. For the past two months he had been complaining of increasing weakness and loss of appetite. For the past month he had been vomiting off and on. A blood chemistry test showed urea 84 mg. The diagnosis was uremia.

Physical examination showed a marked anemia, evident loss of weight; enlarged left ventricle. Abdomen: mass visible in left upper quadrant which appeared to be dilated stomach.

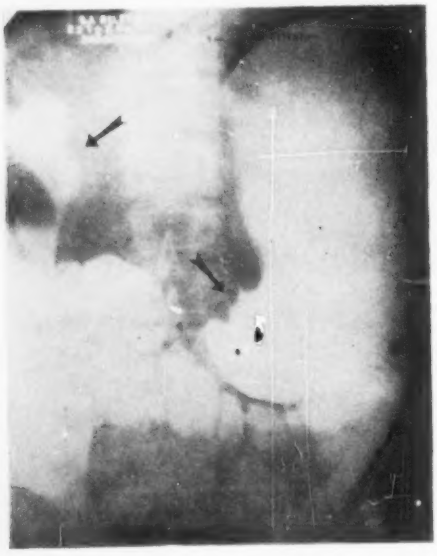
G. I. X-Ray revealed pyloric carcinoma with twenty-four hour retention. (see Figs. 1-2-3). Obviously uremia can account for vomiting and loss of weight, even blood in vomitus and in the stools, so that concurrent gastric carcinoma was entirely overlooked.

A review of the autopsies done at the Greenpoint Hospital for the past twenty-three years was made for the purpose of ascertaining what percentage of the patients presenting gastro-duodenal ulcer or carcinoma had concurrent pathology extrinsic of the gastrointestinal tract which might have been considered the cause of the gastrointestinal complaint. Sixty-two cases were found in which there was gastric carcinoma or peptic ulcer. It might be considered that the advanced age of those coming to autopsy would account in some degree for the multiplicity of pathological findings. The average age of the patients investigated was only forty-one, the youngest twenty-two and the oldest sixty-nine.

Of the sixty-two cases, fifty showed pathology outside of the gastrointestinal tract which if discovered, while the patients were still alive, might have been considered sufficient to explain the gastrointestinal symptoms. In fact in some of these cases an erroneous diagnosis was actually made.

For Example: *Case 121* A: Negro, 50 years old. Admitted 11/8/27. Died 2/20/28. Complaint: Epigastric pain, belching, eructation and backache between scapulae three years.

By physical examination and X-Ray it was determined that the patient had syphilis with mesaortitis luetica and aneurysm of the descending arch of the aorta. During his stay in the hospital he complained bitterly of epigastric pain. There were various speculations as to the cause of this pain, as follows: 1: "Aneurysm of caeliac axis or hepatic artery". 2: "Aneurysm of abdominal aorta." 3: "Aneurysm eroding



Case No. 5. Fig. 2. Pyloric carcinoma with marked 7 hour retention. Calculus rt. kidney.

Case No. 5 Fig. 3. Pyloric carcinoma with marked 24 hour retention. Calculus rt. kidney.

posterior wall of sternum." 4: "Erosion of vertebral column. Reflex epigastric pain." 5: "Gastric Crises." At autopsy the aortic aneurysm of descending arch of the aorta was found, also mesaortitis luetica, but no bony erosions or aneurysms of abdominal vessels. The second portion of the duodenum showed a large ulcer with the head of the pancreas bound in one mass to the ulcer base. No gastrointestinal X-Rays had been taken.

Case 129: E. O., age twenty-two. Pregnant four months, admitted 6/29/30, 11 A. M. The patient had received two doses of neosalvarsan, the last one four days prior to admission. Patient died 5:45 P. M.

Diagnosis: Toxic hepatitis due to neosalvarsan. Autopsy showed toxic hepatitis, also a peretrating ulcer 1x2½ centimeters on posterior wall of cardia four centimeters from oesophageal orifice.

Microscopically there was no evidence that the gastric ulcer was syphilitic. It is conceivable that if this patient had not had lues, and had not received salvarsan, that she still might have had her gastric ulcer and because she was pregnant, the pregnancy might have been considered sufficient to account for her gastric complaints.

Case 2585: H. P., age 45, married, admitted 7/2/28. Complaint: Loss of weight, epigastric pains and "heavy" sensation in stomach p. c. "as if food was not digested." Cough for many years, and palpitation on exertion. Mother died of tuberculosis. Seven months ago she was suddenly seized with a severe attack of epigastric pain which lasted four hours. Three similar attacks since, not as severe as the first. Never vomited. Between attacks has had epigastric distress as described above.

Physical examination: Emaciated patient. Infraclavicular impairment with crepitant rales both sides. Posterior impairment of resonance left upper lobe. Heart: faint mitral systolic. Abdomen: Liver and spleen not palpable, no masses. Extremities: negative. Small shotty glands present in axilla and inguinal region.

Impression: Pulmonary tuberculosis. Temp: 100-102, pulse: 100-120, respirations: 20-25. Blood count: R. B. C. 3,000,000; W. B. C. 10,400; Differential: Polys: 85%; Lymp.: 15%. Chest X Ray: Increased hilum markings upper one third both lung fields. Temperature remained normal for two weeks and patient left the hospital 9/3/28 and returned 9/19/28. Interval history: Since leaving the hospital has been running high temperature daily, the rise occurring in the afternoon. No other complaints. 9/31/28: Massive gastric hemorrhage, transfusion given. 10/4/28, patient died. Autopsy: Chronic adhesive pleuritis. Tuberculous bronchial lymphadenitis. Bilateral apical tuberculosis. Adenocarcinoma on posterior wall of mid-stomach with central ulceration with involvement of regional lymph nodes. Splenic metastases.

In this case the obvious advanced pulmonary tuberculosis seemed sufficient to explain the digestive complaints causing the oversight of a concurrent carcinoma.

Comment

Group IX, which I have designated as Neurosis and Psychoneurosis seems recently to play a rapidly increasing role in producing gastrointestinal symptoms. Although I have compiled no actual figures, it is my impression that in my own private practise at least 30% of the referred patients have gastrointestinal symptoms as a result of neurosis or psychoneurosis. In this particular group I find the recognition of psychoneurosis very frequently results in the overlooking of concurrent organic pathology in the gastrointestinal tract.

Conclusions

1. Pathology of almost any organ may cause gastrointestinal symptoms.

2. It is not uncommon for intrinsic gastrointestinal disease to exist concurrently with pathology extrinsic to the gastrointestinal tract.

3. Despite the finding of extrinsic pathology which seems to account for gastrointestinal symptoms, an investigation of the gastrointestinal tract is always indicated, especially if there is no emergency.

4. Eight cases are cited to illustrate this point.

5. Discussion of sixty-two autopsies at Greenpoint Hospital, in which 80% showed pathology outside of the gastrointestinal tract sufficient to account for gastrointestinal symptoms, and in addition, co-existing intrinsic gastrointestinal pathology.

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AN UNUSUAL DIABETIC COMA IN A CHILD WITH RECOVERY, WITH SPECIAL REFERENCE TO INSULIN RESISTANCE AND HYPOPOTASSEMIA

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IS IT possible to treat a diabetic coma successfully without complete laboratory guide? The answer yes, will depend upon the diabetic's physician's experience in the treatment of comas and his knowledge of interpreting laboratory results as applicable to the condition. It is the belief of the writer that not infrequently the patient's life has been jeopardized when the laboratory results were the sole guide in the interpretation or treatment of the condition.

The primary purpose of recounting this case of a child aged 12 years who recovered from diabetic coma is to report the (1) unusually large quantity of insulin required within a short interval of 11 hours; (2) to emphasize the necessity of observing physical response of the patient and not putting all the reliance upon the laboratory results for the sole guidance of therapy; (3) to indicate the possibility of avoiding frequent or unnecessary laboratory examinations during the period of coma; (4) to show that the level of the blood sugar or the carbon dioxide combining power of the plasma revealed no relationship to the degree of acidosis or coma nor was it a guide to the dose or amount of insulin required; (5) even though the electrocardiographic changes were indicative of hypopotassemia the physical signs or symptoms were insufficient to warrant potassium therapy; (6) to prove the efficiency of the early use of glucose as has also been advocated by various investigators (1,2,3,4) and (7) to show role of alkali in a case with electrocardiographic diagnosis of hypopotassemia.

A twelve year old white female child entered St. Joseph's hospital 1:45 p.m., November 10, 1949 in a comatose state. Four days prior to hospital admission, according to the history obtained from child's mother, the child had been taken to a physician because of marked vulva pruritus, increased thirst and urination, as well as marked weight loss. At infrequent intervals during the past 3-4 months the patient has been suffering from "cramp-like" pains in legs and abdomen. Several hours before the child was brought to the doctor the above symptoms had been associated with loss of appetite, drowsiness and marked weakness as well as nausea and vomiting. Past medical history revealed no knowledge of diabetes in the mother or father's side.

Physical examination revealed a child severely emaciated in an unconscious state lying in bed and markedly dehydrated—mouth, tongue and lips parched, with roughness and generalized dryness of the skin. The breathing was deep with mouth partially open, imparting a pronounced characteristic odor of acetone which was noticeable throughout the room. The eye balls appeared to have receded with marked softness upon palpation.

The abdomen was normal except for some slight distention. The chest and lungs revealed no pathology upon physical examination. With the passing of minutes required for the physical examination the physical signs appeared to become progressively more severe with rapid and labored respirations 30 per minute, and the pulse rapid, 118 per minute, with regular rhythm. Blood pressure 50/20 mm. of mercury, temperature 97.4 F (axilla).

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Laboratory examinations: Upon admission blood sugar was 430 mg. per 100 c. c., (Folin-Wu)., urea nitrogen 12 mg., carbon-dioxide combining power of the plasma 10 volumes per cent. There were 4,700,000 red cells and 20,980 white cells per cu. mm. of blood, the hemoglobin was 92 per cent. Of the white blood cells, 58% polymorphonuclear neutrophiles, lymphocytes, 20%, large mononuclear cells, 2%. The urine was strongly positive for albumin, sugar, acetone, diacetic acid reactions.

Therapy: First three hours; (a) 500 units of insulin (50 units of globin, 450 units of crystalline zinc) was given subcutaneously. (b) Gastric lavage with 5% sodium bicarbonate solution until returns were clear, then 200 c.c. of the solution was allowed to remain in the stomach. (c) 1000 c.c of 5% glucose in normal physiological saline solution given intravenously.

At the end of 3½ hours the patient began to void involuntarily. Her general condition appeared grave, respirations became more labored, dehydration marked, acetone odor was more pronounced; and the pulse volume was poor. Within the following seven hours 6200 more units of insulin were administered, a total of 6700 units in less than eleven hours since the patient had been admitted to the hospital. In spite of the increased insulin dose and continuous administration of intravenous 5% glucose in normal physiological saline solution, acetone odor was still marked. The respiratory difficulties and the dehydration, however, were not as pronounced. Hence 520 more units of insulin were administered within the following 3 hours, a total of 7220 units in 14 hours. Because of vomiting, gastric lavage was repeated with the 5% solution of sodium bicarbonate followed by the administration of two drams of sodium bicarbonate every hour for 8 doses through the gastric tube.

Even though the electrocardiographic changes at the end of 14 hours were indicative of simple tachycardia and the QRS and T wave changes—T waves inverted, Q-T prolonged; S-T's depressed, were suggestive of hypo-potassemia there was not sufficient physical symptoms or signs present to warrant potassium therapy as well as the fact the patient was progressing satisfactorily after the first eleven hours following the administration of large doses of insulin. We were also cognizant of the observations that not infrequently there are cases with low serum potassium levels without electrocardiographic changes of the deficit.

In spite of fact the child was conscious and the respirations apparently normal, slight acetone-like odor was still present. Insulin was again administered within the following ten hours in doses of 50 units hourly for 10 doses plus 50 units of globin insulin with zinc, a total of 7770 units of insulin. (100 units of globin insulin and 7670 units of crystalline zinc insulin) within 24 hours. Within the 24 hour period 4000 c.c. of 5% glucose in normal saline solution was given intravenously and 800 c.c. 2½% glucose in water by hypodermoclysis plus the sodium bicarbonate solution through the stomach tube.

At the end of the 24 hour period the child appeared to have recovered from the diabetic coma—was able to answer questions, had no acetone odor, moist skin, but a slight drowsiness. But in spite of this better condition the child was able to take a small amount of fluids, strained orange juice diluted with water by mouth. The blood sugar level was 310 mg., carbon-dioxide combining power of the blood plasma 54 vol. per cent.

Temperature obtained at this time revealed it to be elevated to 103° (axilla) pulse rapid with increased respiration. These findings appeared to confuse the diagnosis of the condition of the child. The cause of the elevated temperature could not be determined, but within 4 hours after the administration of 30,000 units of crysticillin and an effective soap suds enema the temperature dropped to 99° (ax) and the crysticillin was discontinued.

Thirty four hours after hospital admission the child's tem-

perature and respirations were normal and she was able to follow liquid diet. The insulin was reduced to 20 units of globin insulin for breakfast and 10 units of globin insulin for supper. X-ray examination of chest was negative for pathology.

Upon the day of discharge, 12 days after hospital admission the patient's post-prandial blood sugar was 220 mg., with 20 units of globin insulin for breakfast and 15 units of globin insulin for supper, and she was symptom free. The diet consisted of 120 grams of protein, 80 grams of fat, and 170 grams of carbohydrate, a total of 1880 calories for the day. Two months later the child had gained 12 lbs., and she was symptom-free with a postprandial blood sugar of 223 mg., taking 28 units of globin insulin for breakfast only.

Discussion

It was apparent that a blood sugar level of 430 mg., carbon-dioxide combining power of the blood plasma 10 vol. per cent, urea nitrogen 12 mg., were not sufficiently informative of the degree of the diabetic coma. This was realized within three hours after the administration of 500 units of insulin when the patient's condition appeared grave—with respiration more shallow, pulse rate and dehydration increased, more pronounced acetone, voiding involuntarily. With this picture the dose of insulin was increased from 100 units every 15 minutes for 6 doses to 300 units every 15 minutes for 14 doses (1200 units hourly).

After we had administered 6700 units of insulin at the end of eleven hours, the child became sensitive to the hypodermic needle. She reacted by crying. Since acetone odor, though less pronounced, was still present 120 units of plain insulin were immediately given followed by 100 units every ½ hour for 4 doses. Thus a total of 7220 units had been administered at the end of 14 hours since admission.

Even though the electrocardiographic changes were suggestive of hypo-potassemia we felt that the child was apparently well and lacked sufficient symptoms or signs to warrant potassium therapy. It is our routine that as soon as the patient displays signs of recovery from the coma, to administer liquid diet—strained diluted orange juice or broth, orally or through the nasal or gastric tube. Both are sources of potassium. If vomiting re-occurs we repeat the nourishment following gastric lavage.

It is the opinion of the author that if the initial results of the laboratory examinations were the sole guide of the coma when the patient was first admitted to the hospital he would not have given such large doses of insulin. Apparently the insulin resistance was overcome during the first 10 hours. Sheppard (5) reported a case of a man aged thirty-two years in diabetic coma who recovered after having been administered 56,080 units of insulin. However, his patient was given 1080 units in the first 11 hours. The resistance to insulin was apparently increased after this period as noted by the total 56,080 in 26 hours. It appears in the above case report that if the writer had only given 1000 units of insulin during the first 11 hours instead of 6700 units the outcome would have been fatal to the child.

Boulin and his associates (6) report a case of diabetic coma who recovered after the administration of only or sole therapy of 19,000 units of insulin intravenously within sixteen hours as noted by the return of the alkali reserve to normal from a low level of 19 volume per cent. They administered 1,000 units per hour. Following the recovery from the diabetic coma they noted the temporary appearance of extra-systoles.

In the writer's case the child was given 1200 units hourly. Insulin was not solely given but also glucose and sodium bicarbonate. In Sheppard's (5) case recovery from the diabetic coma was not without reaction or complication. His patient developed hypoglycemic convulsions within 25 hours after the last dose of insulin. He apparently is not in favor of glucose therapy in diabetic coma, as he states that . . . . . "glucose is not an innocuous substance in diabetic coma and that its use as a precaution against hypoglycemia may gravely jeopardize the patient's chance of survival." Micks (7) is also of the same belief, especially when he claims that "glucose must not be given by any route until clinical recovery has been achieved . . . . . "

As based upon the experience of a large number of diabetic comas, the writer disagrees with the above practice against glucose (8,9) and alkali therapy in the initial stage of diabetic coma. No ill effects or added risk have been observed by the writer with glucose or alkali. In spite of the large doses of insulin administered in the case cited the child recovered from diabetic coma without hypoglycemic reactions or apparent physical defect.

In spite of the fact that there were sufficient or combination of factors—loss of appetite, nausea, vomiting, diuresis, dehydration during the pre-coma and coma period without therapy, administration of large doses of insulin, fluids—glucose, saline, water (no potassium)—as well as the excretion of the organic acids in the body by drawing upon the fixed alkali reserve (10) in the above case of diabetic coma, to help bring about a depletion of the potassium electrolyte, the patient was progressively recovering from the diabetic coma. The physical symptoms or signs were not sufficient to institute potassium therapy.

Conclusions

A case of diabetic coma in a child aged 12 years with recovery following the administration of 7220 units of insulin (100 units of globin with zinc and 7120 units of crystalline) within 14 hours—500 units within the first three and a half hours, 6200 units during the following seven hours, and 520 units in the remaining 3 hours, is reported.

Even though the patient had apparently recovered from the coma, acetone-like odor was still detected. 550 more units of insulin were then administered within the following 10 hours to insure more adequate control of the diabetes. After the administration of 7770 units of insulin, at the end of 24 hours, the patient's blood sugar level was 220 mg. per 100 c.c., carbon-dioxide combining power of the blood plasma was 54 volume per cent and the patient was symptom-free.

1. The administration of less insulin within the first three or ten hours might have resulted in an unfavorable prognosis for the child.

2. Recovery occurred without hypoglycemic reactions as amply described under discussion.

3. Physical response—respiratory, ocular pressure, blood pressure, skin changes, pulse rate, presence or absence of characteristic odor of acetone, were the guide to insulin therapy after the laboratory diagnosis had been established.

4. Laboratory examination for the establishment of an accurate diagnosis is essential, but not to be entirely depended upon for the sole guide to therapy.

5. The frequency of the lack of correlation of the

common laboratory examination as blood sugar, carbon-dioxide combining power of the blood plasma, to the degree of acidosis or coma.

6. Potassium or phosphate deficiency without sufficient physical signs of symptoms may not require their respective therapy especially if the patient is progressively recovering from the diabetic coma.

7. Early administration of sufficient insulin, glucose and alkali with careful observation of physical response to therapy is advocated.

8. Advocate feeding of liquid food upon the recovery from coma, as orange juice (strained), milk, broth, etc., orally or through gastric or nasal tube to help correct vitamin deficiency or nutritional disturbance as well as any tendency toward hypopotassemia that not infrequently occurs. If vomiting re-occurs, repeat feeding after gastric lavage.

9. Since deprivation of insulin and not excessive carbohydrate intake brings about glycogen depletion in the liver and causes the development of diabetic ketosis and of the consequent acidosis and coma (11), adequate administration of insulin in diabetic coma becomes vital, while other therapies as glucose, alkali are essential but not vital. Hence early administration of large amounts of insulin as described in the above case has helped reduce the duration of acidosis as well as cause less potassium to be lost.

Approximateiy one year after the patient had been discharged from the hospital her post-prandial blood sugar level was 200 mg., weight 110 lbs., a gain of 29 lbs., upon 30 units of globin insulin for breakfast.

The author takes pleasure in expressing his appreciation to his assistants, Philip Gerber, M. D., Frank Bove, M. D. and Paul L. Carmichael, M. D., Resident physician, St. Joseph's hospital for their valuable aid in the treatment of the child in diabetic coma.

Insulin, crystalline zinc or the plain, used in the above case was that of Eli Lilly and Co., and E. R. Squibb and Sons; Globin insulin with zinc was that of Burroughs Wellcome & Co.

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GASTROINTESTINAL HEMORRHAGE DUE TO RUPTURED ABDOMINAL AORTIC ANEURYSM

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OCCASIONALLY, the physician encounters hemorrhage from the gastrointestinal tract which is not due to the well known common causes such as peptic ulcer, esophageal varices, blood dyscrasias and gastrointestinal neoplasms or ulcerations. As early as 1833, Chanel and Dalmas (1) listed gastrointestinal hemorrhage as a complication of ruptured abdominal aortic aneurysm. In 1943, Rottino (2) compiled a series of 31 cases described up until that time by various authors and, in 1946, Hunt and Weller (3) reviewed a total of 41 reported cases. The latter authors found the incidence of ruptured abdominal aneurysm more common in males in the ratio of 6:1, and that the age range is from 20 to 81 years with an increasing incidence beginning in the sixth decade. The majority of these aneurysms are located just below the origin of the superior mesenteric artery and the most common site of rupture is into the third portion of the duodenum (29 of 41 cases, or 71%). This they attributed to the close fixation of the third portion of the duodenum to the anterior aortic wall. Pain is usually the chief complaint, and it may be epigastric or lumbar in location. Although hematemesis and melena are at times terminal features only, there may be bleeding for days or weeks prior to the final massive hemorrhage. Physical examination may reveal an expansile abdominal mass, the presence of which is confirmed by means of roentgen visualization of a localized calcific area with vertebral erosion (4). Laboratory studies may reveal a high leukocyte count and moderate elevation of the diastase level of the urine (5).

Because of the rarity of this lesion we feel that the following case report should be added to the literature.

From the Gastrointestinal Section, Department of Internal Medicine, Medical Center, Jersey City, N. J.

Case Report

J. H., a 59 year old white male, was admitted to the Jersey City Medical Center on January 14, 1949, complaining of pain in the left leg and melena. He had apparently been well until one and one-half hours prior to admission when he was aroused from sleep and had a bloody, watery bowel movement. This was associated with numbness, pain and inability to move the left leg. Motor power returned shortly but the pain and numbness persisted. Six months previously the patient had a gastrointestinal upset characterized by diarrhea and gaseous eructations lasting about two weeks. He

thought that this episode was due to the ingestion of "bad" pork. An amputation of the right leg had been performed ten years before admission for osteogenic sarcoma.

Physical examination revealed a moderately well developed and nourished white male with a blood pressure of 115/65 and normal temperature, pulse and respirations. There was a mature cataract in the left eye; the lungs were clear to percussion and auscultation and the heart revealed only a blowing systolic murmur at the apex. There was a non-tender, pulsating mass in the abdomen found slightly below the umbilicus in the mid-line and fresh blood was found upon digital examination of the rectum. The right leg had been amputated at the upper third of the thigh and the left leg was cold and pale below the knee. Both femoral pulses were palpable but the dorsalis pedis, posterior tibial and popliteal pulses were absent in the remaining leg. There were 3.9 million red blood cells and 13,500 white blood cells per cu. mm. Blood serological tests for syphilis were negative. The blood sugar was 145 mg. per cent and the non-protein nitrogen was 42.5 mg. per cent.

The patient was transfused with whole blood upon admission but a few hours later he went into shock and had a tarry stool. His condition improved with further transfusion therapy but 24 hours after admission another similar episode occurred and the patient expired.

Post-mortem examination (performed by Dr. Angelo Gnassi) revealed an aneurysm of the abdominal aorta just below the superior mesenteric artery with erosion of the adjacent lumbar vertebrae. The third portion of the duodenum was adherent to the aneurysm which had perforated into the duodenum. The immediate cause of death was massive hemorrhage into the bowel from the aneurysm.

Summary

A case of ruptured abdominal aortic aneurysm with perforation into the third portion of the duodenum producing massive gastrointestinal hemorrhage is reported.

Except for the absence of abdominal pain, the symptoms and findings were similar to those in previously reported cases.

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ACUTE HEMORRHAGIC PANCREATITIS

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THE acute onset of hemorrhagic pancreatitis, the dramatic suddenness with which it strikes and the relentless course it may take regardless of all therapeutic endeavors has baffled many observers. The etiology of the disease has remained obscure in spite of many theories proposed (1,2,3). If one or more etiologic factors were known it would seem conceivable to prevent either the onset of the disease or to alter its course favorably.

Recent experimental work by Popper et al (4) has indicated that when pancreatic cells are damaged by pancreatic duct ligation and injection of secretin, any additional ischemic insult, such as transient interruption of the arterial blood supply, may produce a change of the pancreatic edema into hemorrhagic necrosis. It appears that experimental pancreatic damage will lower the resistance of the cells to the action of pancreatic enzymes to such an extent that any additional ischemic insult will initiate cellular autolysis and the course of events known as hemorrhagic necrosis.

If such experimental results were applied to human pathology one would have to presume that so called acute hemorrhagic pancreatitis may be the result of two etiologic factors acting concurrently: 1. Chronic pancreatic disease, the counterpart to experimental pancreatic damage, and 2. Demonstrable pancreatic ischemia, the counterpart to the temporary experimental interruption of the arterial blood supply. Clinically, such transient pancreatic ischemia may be anticipated as the result of drop in arterial blood pressure, shock, diminution of cardiac output, passive hyperemia, or mesenteric thrombosis.

It is just such a case the author wishes to present here thus furnishing clinical support to the validity of conclusions drawn from experimental studies.

From the Medical Department of the Chicago Memorial Hospital and from the Medical and Gastro Intestinal Research Department of Michael Reese Hospital, Chicago, Illinois.

Submitted March 15, 1950.

Case Report

Mrs. V. S. aged 54, was admitted to the Chicago Memorial Hospital May 18, 1949, through the courtesy of Dr. R. B. Edelstein. Her past history was insignificant with the exception of occasional transient mild upper abdominal distress and nausea which was ascribed by the patient to a nervous stomach or possible gall bladder attacks, but was never thought serious enough to warrant closer investigation. The present disease started abruptly two days prior to hospital admission with severe upper abdominal pains, nausea and vomiting. Her condition became progressively worse. Rapid development of abdominal distention, fever, dehydration and absence of bowel movements prompted hospitalization.

Physical examination revealed a well nourished patient, apparently acutely ill, prostrated and perspiring freely. The face was flushed, there was cyanosis and dyspnoea, the hands were cold and clammy. The temperature was 101° F., the arterial blood pressure was 95 millimeters mercury over 70. Significant findings were the presence of coarse and moist crepitant rale over both lower lung fields. The heart did not seem enlarged. Its action was grossly irregular and rapid, averaging a rate of 160, the sounds were of poor quality, mur-

murs were not discernible. The abdomen was markedly distended, there was generalized rigidity with a maximum point of tenderness over the left mid and upper abdomen. Auscultation over the abdomen disclosed hyperactive bowel sounds and borborygmi. There was no evidence of ascites. The remainder of the physical examination was negative.

Laboratory findings revealed the urine to contain two plus albumin without other significant abnormalities. The red blood cell count was 3,500,000, the hemoglobin 11.2 grams, the leukocytes amounted to 13,300 with 81 per cent polymorphonuclears. Blood chemistry findings were as follows: Serum amylase 416 units (normal value 70 to 160 units), serum lipase 231 units (normal value 40 to 140 units), serum chlorides 534 m. e./L., serum bilirubin 1.33 mgm%, NPN 42 mgm%, and carbon dioxide combining power 66 mM/L. An X ray film of the abdomen was not contributory to diagnosis with the exception of a group of small concretions in the right lower abdomen, possibly gall stones. The electrocardiogram showed coarse auricular fibrillation with a very rapid ventricular rate, averaging 200. QRS was upright in all limb leads, small in lead 1 and 3, ST was depressed in CF4, the T waves were upright in limb leads, tall in CF2, and small in CF5.

Course: The high values of blood amylase and lipase and the characteristic clinical picture rendered the diagnosis of acute pancreatitis certain. Because of obvious evidence of shock and peripheral vascular failure shock treatment was instituted immediately. This consisted in blood transfusions and replacement of electrolytes. A surgical consultant recommended conservative management. A Miller-Abbott tube was inserted to decompress the markedly distended intestines. Rapid digitalization with digilanid resulted in transient conversion of auricular fibrillation to sinus rhythm and diminution of the rapid rate. However the temporary improvement soon gave way to a steady deterioration of the condition. The abdomen became more distended and bowel sounds were no longer audible. A bluish-purple discoloration around the umbilicus (Cullen's sign) became manifest. The patient became restless and disoriented. At the fifth hospital day the temperature rose to 106° F., the patient became comatose and died in convulsions.

Autopsy (only the essential findings are given) performed by Dr. Otto Saphir: The peritoneal cavity contained approximately 300 cc of cloudy dark and hemorrhagic fluid. There was widespread fibrino-purulent peritonitis with fat necrosis. A cystic mass was present in the region of the tail of the pancreas, containing several hundred cc of fluid and clotted blood. The cystic wall was lined by organizing blood clots and was partly formed by the anterior surface of the tail of the pancreas. The head and body of the pancreas was largely replaced by yellow and green necrotic material and massive areas of blood clots. The pancreatic duct near the ampulla of Vater was dilated for a distance of 3 cm. The distended gall bladder was filled with 50 to 60 small yellowish calculi. Many stones were impacted in the cystic duct. A single small calculus was present in the common duct. There was phlebothrombosis of portal, hepatic, and superior mesenteric veins. The heart was of average size and shape. There were several small subepicardial hemorrhages at the base of the heart near the auriculo-ventricular groove. There were no significant gross myocardial or valvular changes. Histologically, however, moderate perivascular fibrosis, edema, and fat infiltration was seen in the myocardium. Considerable chronic passive hyperemia of the visceral organs, including the lungs, was present. The histologic examination of the pancreas showed large areas replaced by amorphous shadow structures sometimes stained red and other times yellow or blue. In some areas recent hemorrhage was noted. In other areas large foam cells were present. Sometimes phagocytic cells were encountered showing many granules of debris in their cytoplasms. Areas of necrosis were sharply demarcated from the remaining pancreatic tissue. The pancreas, not involved by the necrotic process, disclosed relatively small acinar cells with granular pink or blue cytoplasm and hyperchromatic or pyknotic nuclei. There was a moderate interstitial fibrosis. In many areas there were proliferated lining cells of the ducts. The lumens of other ducts were dilated and contained amorphous debris or desquamated lining cells. A few ducts were encountered which were lined by stratified squamous epithelial cells. The islands of Langerhans showed no changes.

COMMENT

Acute hemorrhagic pancreatitis is commonly regarded as a disease striking with acute suddenness in an apparently healthy individual. Recent experimental work (4) has indicated that in the presence of a damaged pancreas hemorrhagic pancreatic necrosis can be produced by interference with the arterial blood supply. Our case, as described, seemed to support the validity of these experimental conclusions. There was histologic evidence of cellular pancreatic damage in those areas of the pancreas not destroyed by the hemorrhagic necrosis. There was chronic calculous gallbladder and biliary tract disease, so frequently found to be a forerunner of or to accompany chronic pancreatic disease. Because of the presence of stones in the gallbladder, the dilatation of the proximal portion of the pancreatic duct and because of the finding of metaplasia of the lining cells of an occasional duct, combined with interstitial fibrosis, it is obvious that the pancreas was damaged prior to the event of acute necrosis. Experimental evidence further postulates that additional pancreatic ischemia must exist, at least temporarily, before hemorrhagic necrosis can occur. Our case offered ample clinical and pathological evidence for such transient ischemia. The patient was in severe myocardial failure with an apparent reduction of cardiac out-put and peripheral blood flow. There was auricular fibrillation and shock. There was post mortem evidence of venous thrombi in hepatic, portal, and mesenteric veins, presumably the result of reduced blood flow and venous stasis.

It seems unwise to draw conclusions from one case. However, if further case reports should bear out similar deductions it would support the assumption that acute hemorrhagic pancreatitis is the result of a sudden or transient ischemia insult upon a previously damaged pancreas. If this be true it would seem important to demonstrate pancreatic damage in such "exposed" individuals. Recently, sensitive pancreatic function tests have been devised (5) which may make it possible to screen possible "candidates" for hemorrhagic pancreatitis. Such individuals should be protected from vascular insults as far as possible. If such efforts would succeed in either preventing the onset of the disease or in altering its course favorably it would render distinctly hopeful an otherwise gloomy outlook.

SUMMARY AND CONCLUSIONS

Recent experimental studies have indicated that human acute hemorrhagic pancreatitis may be the result of an ischemic insult upon a previously damaged pancreas. A case of acute hemorrhagic pancreatitis is reported presenting clinical and post mortem evidence to support the validity of the aforementioned experimental conclusions. It is suggested that individuals with diminished pancreatic function be protected from vascular insults as far as possible.

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ABSTRACTS ON NUTRITION

KOENIGSFELD, E. G. H.: *Nutritional macrocytic anemia and histamin-fast achlorhydria.* (J. Indiana Med. Assn., 18, 8, 276-278).

Of 18 persons with nutritional macrocytic anemia, 11 showed histamin-fast achlorhydria. The anemia was due to low protein intake (vegetarianism). Histories showed a high incidence of ascaris infestation. Fair results were obtained from the use of crude liver extract injections. Folic acid was not used.

FRAZER, A. C.: *A new mechanism of vitamin deprivation.* (Brit. Med. J., Oct. 1, 1949, 731-733).

We know from studies on sprue that riboflavine, nicotinic acid and/or pyridoxin deficiency symptoms may appear at irregular intervals and are quickly cured by parenteral administration of the appropriate vitamin or by very large oral doses. After finding greatly increased numbers of bacteria in the high gut in sprue (and this obtains also in pernicious anemia) the author advances the hypothesis that there is a competition for vitamins between the bacteria and the diet. Actually, the stools in sprue often contain more vitamins than the diet. The metabolic demands of a varying but essentially non-pathogenic flora may be the key to the problem of the multiple but selective vitamin deficiencies so commonly observed in these conditions. Until more is known about this "competition for vitamins" it appears obvious that such patients, especially at times when deficiency symptoms appear, should receive parenteral vitamin B-complex preparations.

STRIKER, C.: *Diabetes mellitus—an orientation.* (Texas State J. M., Sept. '49, 45, 9, 617-622).

Striker regards as the chief experimental "leads" in diabetes the following.—alloxan diabetes, isotropes, insulinase, experimental arteriosclerosis, and the Houssay dog (pituitary diabetes). Diabetes is more than a disease of the pancreas. Mirsky has demonstrated an anti-insulin substance. The administration of sex endocrine products to pregnant diabetics appears to reduce infant mortality in the new-born, but equally good results may be obtained by extraordinarily careful management without sex hormones. Hypoglycemia comes on suddenly, coma more slowly. Hypoglycemic reactions may occur with high blood sugar, and fail to occur with a blood sugar of 22 mg. per cent. It is the speed of the drop in blood sugar level that produces the reactions. Striker does not think that a cause-effect relationship exists between hyperglycemia and degenerative changes, but that the latter are due to the *length of time* diabetes has been present. He is not convinced that the level of blood sugar is an important aspect of the control of diabetes. He is neither a Tolstoi "free-dieter", nor does he recommend the Joslin-type of food restriction. He reviews the aims of diabetes detection drives and the work of the American Diabetes Association. Diabetes has became a public health problem.

KOSZALKA, M. F. AND LEVIN, J. J.: *Idiopathic hyperlipemia.* (Ann. Int. Med., 33, 2, 473-480).

The authors describe a case of idiopathic hyperlipemia with hepatomegaly and lipemia retinalis in an adult. The diagnosis was confirmed by analysis of the serum lipids and by bone-marrow and liver biopsies. The clinical picture was characterized by milkiness of the serum, lipemic appearance of the retina and by recurrent episodes of lower substernal pain radiating into the entire abdomen and throughout the chest. (The cause of this pain is not explained but may have been due to liver engorgement which accompanied each attack). A low fat diet was effective in preventing recurrences of the acute attacks of abdominal pain. The degree of lipemia, retinalis, the hyperlipemia and the liver engorgement were dependent upon the amount of fat eaten. Neutral fat was 3440 mg. per cent (normal 0-150 mgm).

HARLAND, J. C., HUMBLE, J. G. AND MANN, P. G.: *Diphyllobothrium infestation and anemia in Great Britain.* (Brit. Med. J., July 22, 1950, 188-192).

A Finnish domestic servant, aged 22, presented dyspnea and occasional morning vomiting. Her pallor led to a blood examination which revealed hemoglobin 60 percent, red blood cells 2,500,000, color index 1.2, and a mean corpuscular diameter of 8.34, all consistent with a diagnosis of Addisonian P. A. The bone marrow smear, however, was not consistent with P. A. in relapse possibly because the patient had already received an injection of liver extract. A histamine-fast achlorhydria was present. Stool examination revealed diphyllo-bothrium (fish tapeworm) ova, and treatment with male fern expelled two adult worms intact. Without further treatment the patient rapidly recovered from the anemia and became normal. The available evidence indicates that it is the live worm in the intestine which causes anemia by interfering with the formation of hemopoietin. Patients with the disease have been shown to possess intrinsic factor. Human infestation with fish tapeworm is practically unknown in England but common in the Baltic States. Only Finns ever develop the megaloblastic anemia.

MOSBECH, J. AND VIDEBAEK, A.: *Mortality from and risk of gastric carcinoma among patients with pernicious anemia.* (Brit. Med. J., Aug. 12, 1950, 390-394).

In 391 cases of pernicious anemia during the period January 1928 to June 1949, there were 115 deaths, as compared with an expected normal death rate of 117. Female patients, specifically treated, have the same chances of survival as normal females, although in males there is a slightly higher mortality. Twenty-one patients died of cancer, a figure which corresponds to the expected number of cancer deaths, but 14 died of cancer of the stomach, whereas the expected mortality from this cause was only 5. In other words, there was an incidence of gastric cancer of 5 per cent, as against an expected incidence of 1.7 per cent. The site of the cancers in the stomach is not confined to the fundus. The cause of the high incidence of gastric carcinoma in pernicious anemia is unkown, but the authors point out that achlorhydria is common to both diseases.

GOFMAN, J. W., JONES, H. B., LINGREN, F. T., LYON, T. P., ELLIOTT, H. A. AND STRISOWER, B.: *Blood lipids and human atherosclerosis.* (Circulation, II, 2, 161-178).

By means of the ultracentrifuge, various lipoid molecules can be floated to the top of the cell and a certain group, designated Sf 10-20, containing cholesterol-bearing lipid and lipoprotein molecules were found to be increased in patients having clinical evidence of atherosclerosis. These molecules bear no relationship to acute alimentary lipemia, nor can their presence be predicted from the analytic total serum cholesterol level. Partial dietary restriction of fat and cholesterol in man results in a gradual decrease in the serum level of such molecules over a period of weeks to months. The presence of these molecules, with molecular weights in the neighborhood of 3,000,000, with increased frequency in myocardial infarction, diabetes, the nephrotic syndrome, hypothyroidism, hypertension and coronary insufficiency, supports the hypothesis of their association with atherosclerosis.

BALFOUR, D. C., JR., HIGGINS, G. M. AND WOODS, K. A.: *A factor in neutralized human gastric juice which prolongs survival of gastrectomized rats.* (Proc. Staff Meet. Mayo Clin., 25, 15, 434-441).

Studies on the gastrectomized white rat, rats which have undergone esophagoduodenostomy leaving an intact stomach, and the normal rat united in parabiosis to a gastrectomized rat, indicate that some unknown deficiency gradually develops after total gastrectomy in the rat. This deficiency results in a hypochromic microcytic anemia and a decline in weight which begins about 6 to 12 weeks after gastrectomy and causes early death of the animal in six months to one year after operation. Neutralized human gastric juice contains a factor or factors which when given orally prevent the decline in weight and prolong the life of these animals. Additional iron therapy is also essential for the gastrectomized rat. Stool analyses show that the effect of neutralized gastric juice is independent of any lack of absorption of food. The benefit obtained by giving neutralized gastric juice seems to last about 12 weeks after therapy is stopped. Hyperplasia

of the squamous epithelium of the esophagus occurred in all gastrectomized rats sufficient to cause obstructive symptoms. Such hyperplasia did not occur in the parabiosed gastrectomized animal, and it was delayed in the other gastrectomized rats by the administration of neutralized gastric juice.

PATTON, A. R.: *Present status of heat processing damage to protein foods.* Nutrition Reviews, 8, 7, 193-196).

Patton believes that the effect of heat processing on the nutritive value of food proteins is a matter of practical importance. Heating food products which contain both protein and carbohydrate tends to cause loss of amino-acids, particularly lysine. A new lysine linkage is formed which is either not digestible by enzymes or is so slowly digested that part of the lysine enters the blood stream too late to participate with the rest of the assimilated amino acids in tissue formation.

LOWREY, G. H.: *Coexistence of diabetes insipidus and diabetes mellitus in a seven year old girl.* (Am. J. Dis. Child., 80, 1, 69-74).

Prior to this report only 2 cases of children showing simultaneously both forms of diabetes have been reported, although 25 cases in adults are recorded. A girl of seven presented inordinate thirst, frequent passage of large volumes of urine and weight loss. On admission, the low specific gravity urine (1003) showed sugar only once, but after concentration by the use of beta-hypophamine (pitressin), sugar appeared and the glucose tolerance test was diabetic in type. On treatment for d. mellitus by insulin and diet and simultaneous treatment for d. insipidus by daily injections of pitressin, the patient is growing normally and seems well. There is encephalographic evidence of some neural degenerative process and, though this cannot be defined, it may be responsible for both diseases through possible involvement of the hypothalamus. On the other hand, the association of the two diseases may not be greater than would result from pure coincidence.

LAMAR, C. P.: *Insulogenic lipodystrophies: their relationship to "brittle" diabetes and to insulin resistance.* (J. A. M. A. Apr. 29, 1950, 142, 1350-53).

Lamar describes 4 cases of long-standing diabetes in whom the insulin injections had been made in such restricted skin areas as to have given rise to fat atrophy and/or hypertrophic and inflammatory lesions. Two of these cases had experienced some insulin resistance which at once disappeared when fresh sites for injection were chosen. The other two seemed to be examples of "brittle" diabetes with rapid and unpredictable alterations in blood sugar levels. They likewise became "normal" diabetics when the over-used sites of injection were discarded. Perhaps allergy and hepatic dysfunction may combine to explain the development of insulogenic lipodystrophies. The author presents a simple schematization for the suitable selection and rotation of injection sites.

COZEN, L.: *Charcot joints secondary to diabetes mellitus.* (Am. J. Roentgen and Rad. Ther., 64, 2, 277-279).

Cozen reports two cases of diabetes who presented neuropathic ankle joints. The x-ray pictures were characteristic of Charcot joints and syphilis was ruled out by spinal fluid examinations. Vibration sense, position sense and ankle reflexes were all diminished or absent. Pain was conspicuous by its absence in spite of the fact that the lesions in both cases were complicated by infection and osteomyelitis. Both cases did well on insulin and penicillin. Probably neuropathic joints are commoner in diabetes than usually considered. In lues the feet seldom are affected, but the feet are affected in all cases of diabetic Charcot joints thus far reported.

Salt-free and rice diets for hypertension. (Practical Therapeutics Section, G. P., 11, 2, 71-73).

A brief review is presented, in general terms, of what is known about the effects on high blood pressure of salt-free and rice diets. The general conclusion is reached that, under the most favorable conditions of treatment where salt can be strictly controlled, less than 20 percent of hypertensives derive any benefit from such treatment. A low calorie diet may sometimes succeed. A low protein diet has no good scientific background and should be avoided. The low-cholesterol diet may possibly do good, but insufficient is known with respect to its effects. Fortunately many people with a systolic pressure of over 200 mm. of mercury may live comfortably for 10 or 15 years without any special treatment.

EDITORIAL

PHYSICIANS AND POPULAR MEDICAL LITERATURE

POPULAR MEDICAL LITERATURE has come to stay. Shall we continue to permit the bulk of this writing to be done by professional craftsmen whose knowledge of medicine is second-handed, or shall we insist that medical men take on the job? In deciding this question we must consider the doctor-author, the medical profession as a whole, the public who devour popular medical literature, and the publishers,—especially the publishers of the countless 'digests' almost all of which contain articles on health.

A rather high percentage of physicians are capable of producing good popular articles dealing with various aspects of health and disease, but they are usually restrained from doing so because there is still a feeling that the practice is not quite ethical.

A little reflection might serve to change this attitude of the profession. The popular worship of medical science is based on hope. This hope has not been thwarted, thanks to the acumen of medical science in the production of useful medicinal substances and techniques. But many of the patients we see in our offices have been previously educated, not by us, but by professional writers who have taken to their bosoms such phases of medicine as nutrition, geriatrics, and psychology, as well as others. Pick up a 'digest' from a news stand, glance through it, and discover that a large industry flourishes today on the fringes of medicine. These professional writers, who are not physicians, have usually been careful to verify their facts so that few erroneous statements appear. Having made this admission, we hasten to aver that however factual their material may be, there is a difference between such medical education and that which might be produced by writers who are also doctors.

Here is one of the points of contact where we physicians have long been losing our hold on the public. A true perspective of a medical problem can only be presented by a physician. A writer who is not a doctor of medicine, usually places emphasis on various aspects of disease which are often at variance with seasoned medical opinion and judgment. Thus there is a definite tendency to impart to the reader an unwarranted emotional attitude toward procedures which deserve merely hard-headed selection and decision. Dietetics is often rendered absurdly complex. Psychology is employed feebly and ineffectively because of lack of background, and because no written article can do what only an interview can do. Geriatrics is sometimes converted from a reasonable subject into an excuse for unjustificable inspirationalism. Read only

a dozen of these small monthlies, and such facts become apparent.

The people who read most of these little journals are past middle age. This statement is confidently made, because the material in them is obviously selected for the particular titillation of an aging population. Elderly people of course have a perfect right to read whatever they wish, and publishers an equal right to provide satisfactory material for them. But unless physicians can find some way of controlling this monthly deluge of medical literature, we are not only going to weaken our hold on the public but remain remiss in what appears to be a duty, viz., to provide popular medical writing of the highest grade. *Hygeia* and *Diabetes Forecast* are aimed at the accomplishment of such a purpose, and while both leave nothing to be desired, they do not, and naturally cannot, sufficiently absorb the field.

Popular magazine publishers are indifferent as to the source of their manuscripts, so long as they are not technically in error and have good reader appeal. The letters, M. D., after a writer's name would lend the article authority and interest provided, first, that the physician-author was either well-known or 'sponsored', and, second, that he was capable of employing popular idiom and an easy style of writing.

The American Medical Association, more conscious now than ever before of the importance of public relations, probably recognizes that popular magazine medicine actually is a problem which ought to belong to the profession. Unless the matter receives the intelligent and careful attention it deserves, the public will keep on drifting further out of our influence. The people will be indoctrinated with ideas which while not necessarily false, lack suitable medical proportion, and practitioners are going to be increasingly irritated by the pseudo-education of their patients.

A Bureau of the A. M. A. could easily be set up for the receipt and distribution of popular articles on medicine. As a legitimate literary agency in contact with publishers, such a Bureau would find no difficulty in establishing a re-write department; all articles would be edited and finally submitted to the authors for approval before release. Publishers of popular magazines would be quite willing to deal directly with such a Bureau, and would welcome such an agency, provided a suitable literary style was attained. This could be assured by employing professional writers under the aegis of the Association. The authoritativeness of the material produced would naturally be beyond question under these circumstances and once the A. M. A. undertook the task, the question of ethics would vanish, at least for most physicians. The doctor of medicine would feel at liberty to address the public through this channel, provided he had something he wanted to say. The chief value of such a plan would consist in providing our aging public with material having the imprint of truth and seasoned judgment, and they deserve as much.

BOOK REVIEWS

Principles of Internal Medicine. T. R. Harrison (Editor in Chief). 1590 pages. The Blakiston Company, Philadelphia, Pa., 1950, $12.00.

This unusual, highly attractive treatise is composed of 7 Parts, the first 5 of which cover the *functional* approach to the principles of internal medicine, and the last 2 of which deal with specific infectious diseases and diseases of organ systems. There are sections on pain, weakness, shortness of breath and cough, indigestion and jaundice, alterations in weight, fluid and electrolyte balance, reactions to injury and stress, etc. There is an excellent section on nutritional disturbances. The book might be said to be a Practice of Medicine, written with physiological principles constantly in mind, and with the advantage of an approach possible only to a series of capable monographs. Unless we are mistaken, this masterly volume will, at an early date, make for itself a permanent place in the libraries of most internists.

Cancer of the Colon and Rectum: Its Diagnosis and Treatment. Fred W. Rankin, B. A., M. D., and A. Stephens Graham, M. D., M. S. 427 pages, Charles C. Thomas, Springfield, Ill., 1950, $7.50.

From the surgeon's standpoint, this text leaves nothing to be desired, for it furnishes in brief enough form all that it is necessary to know about the diagnosis, prognosis and surgical treatment of colonic and rectal carcinoma. The sections on anatomy, physiology and pathology represent a particularly fine contribution to the subject of intestinal malignancy. Treatment, which occupies over half the text, reflects the first-hand experience of the authors and is extremely valuable to the operator. Mortality figures for these operations are below 3 per cent in the hands of mature surgeons. The authors recommend that general practitioners become experienced in the use of the proctoscope.

GENERAL ABSTRACTS

Smyth, J.: *The use of the Harris tube for intestinal intubation.* (Med. J. Australia, May 27, 1950, 698-700).

Smyth has found the single-lumen, mercury-weighted tube of Harris superior to the Miller-Abbott tube and all others. With it he was able to enter the duodenum in 95 per cent of cases, whereas success with the Miller Abbott tube ranges from 60 to 82 per cent and usually less. The Cantor tube is the nearest rival to the Harris tube, but it is stiffer and requires a special terminal bag. The Harris bag can be replaced by an ordinary condom.

Raffle, R. B.: *Sjogren's disease associated with a nutritional deficiency syndrome.* (Brit. M. J., June 24, 1950, 1470-71).

A case is presented of a woman 50 years old who showed the xerostomia and bilateral parotid gland enlargements characteristic of Sjogren's disease, although no ocular symptoms were, as yet, manifest. Treatment was aimed successfully at combatting an associated vitamin and iron deficiency, indicated by angular stomatitis and cheilosis. Difficulty in swallowing resembled the Plummer-Vinson syndrome, and improved. The author believes the deficiency was due to

difficulty in eating, caused by the excessively dry mouth. It is difficult to differentiate, at times, between Sjogren's and Mickulicz's disease.

ROBINSON, J. W., TWADDELL, D. N. AND HAVENS, W. P.: *Homologous serum hepatitis.* (Ann. Int. Med., 32, 6, 1019-1027).

Between 1942 and 1947 at the Pennsylvania Hospital, 15 patients contracted hepatitis after transfusions of pooled plasma and/or whole blood, and 3 of them died. During a 19 month period, six out of 621 (0.96 per cent) recipients of pooled plasma contracted homologous serum hepatitis. Although the incidence of the disease was low, the potential ieterogenic capacity of the 64 pools of plasma made during this time was high, since a minimum of 5 (8 per cent) and a maximum of 10 (16 per cent) were presumably infected with hepatitis virus.

CATES, H. B.: *Massive hemorrhage from peptic ulcer: prognosis and treatment conclusions drawn from a large series treated in a municipal hospital.* (Ann. Int. Med., 32, 6, 1144-1152).

Among 41 patients dying of hemorrhage from ulcer, 38 were over 45 years of age. A clinical survey of 47 patients having bleeding peptic ulcer disclosed no fatalities in those under 50 years of age. Massive hemorrhage from gastric ulcer is twice as fatal as from duodenal ulcer. The usual complications accompanying bleeding ulcer were bronchopneumonia, coronary thrombosis and perforation. Anemia may precipitate coronary insufficiency. The older patients are in the greater danger from hemorrhage, and unfortunately there are no completely satisfactory signs to confirm a persistent shock.

O'NEILL, T.: *The dumping syndrome: an operation for its prevention.* (Brit. Med. J., July 1, 1950, 15-18).

Post-gastrectomy syndrome (dumping) is mechanical in origin and represents one type of jejunal response to precipitate gastric emptying. The dumping syndrome was more common following the Polya than the Hoffmeister-Finsterer operation, since, in the latter, the valve deflects swallowed food and delays its entrance into the gut. The author's operation places the stoma in the center of the cut end of the stomach with a valve above and one below, and a suturing of the jejunum to the stomach for a distance of one-half inch. Among 50 patients on whom the O'Neill technique was used, no severe "dumpers" were found, in fact, only 3 moderate cases.

ALEXANDER, G. H. AND ALEXANDER, R. E.: *The use of gastric mucin as a barium suspension medium.* (Radiology, 54, 6, 875-877).

The addition of 2 grams of mucin to 250 c.c. of barium mixture containing 125 gm. of barium sulfate produced a contrast medium which has the property of more clearly defining small bowel patterns. Thus far, gastric mucin has been used only on normal subjects.

MAGNUSSON, J. H., LAURELL, G., FRISELL, E. AND WERNER, B.: *Aureomycin treatment of infantile diarrhoea and vomiting.* (Brit. Med. J., June 17, 1950, 1398-1400).

An investigation at the Sachs Hospital for Children in Stockholm revealed the presence of a special strain of *B. Coli* (B. Coli neapolitanum) in the stools, and at times in the respiratory tracts of babies suffering from infantile diarrhea and vomiting. Eight such cases were treated with aureomycin with marked success. After a few doses the B. C. N. disappeared from the stools. The clinical condition also improved.

LOGAN, G. B.: *Prognosis of chronic hepatitis in children.* (Proc. Staff Meet. Mayo Clin., 25, 11, 299-304).

About three-fourths of 53 children with chronic disease of the liver died within a period of 5 years after the onset of the disease. One patient, however, lived for 23 years after the onset. Seven patients were still living, six years after the onset of disease. Chronic hepatitis may, in certain instances, be a reversible disease, but further observation is required to make sure that these do not merely represent instances of long latent periods.

PERKINS, R. F., BAGGENSTOSS, A. H. AND SNELL, A. M.: *Viral hepatitis as a cause of atrophy and cirrhosis of the liver.* (Proc. Staff Meet. Mayo Clin., 25, 11, 287-298).

Perkins analyzes 130 cases in which liver atrophy was noted at autopsy, to determine how many were due to viral hepatitis. He felt that 36 of the cases represented instances of viral hepatitis (formerly known as "catarrhal jaundice"). What starts out as viral hepatitis may eventually become cirrhosis. When the liver is injured the result is *regeneration*, and the extent and type of regeneration determines the category into which a given lesion will be placed. From a statistical angle, at least, there is very little evidence to support the belief that hepatitis frequently terminates in cirrhosis, and the matter will require much more study to settle it.

ARTZ, C. P. AND GANTS, R. T.: *Prolapse of redundant gastric mucosa.* (U. S. Armed Forces Med. J., 1, 6, 639-647).

The authors indicate that prolapse of gastric mucosa through the pylorus is being increasingly found and reported. In the case here reported the patient had a long history of dyspepsia and hemorrhages and finally had daily vomiting, at which time an x-ray diagnosis was possible. The characteristic x-ray appearance is an umbrella-like dark shadow at the base of the duodenum. Those who do not respond to ulcer-type medical treatment should have a resection of redundant mucosa combined with pyloroplasty.

MOLNAR, C. J., JR.: *Fibrocystic disease of the pancreas.* (U. S. Armed Forces Med. J., 1, 6, 629-638).

Molnar shows that fibrocystic disease of the pancreas composes one group of the so-called celiac disease. One of the debated problems is the cause of the invariable, severe respiratory infections which usually terminate life before 14 years of age. The Andersen school attributes this to faulty absorption of vitamin A. The chief diagnostic sign is an absence of trypsin in the duodenal secretion. Meconium ileus is the characteristic finding in the newborn. He describes a case in a girl of 5 who died as the result of overwhelming respiratory infection showing, at autopsy, bronchopneumonia, bronchiectasis and pulmonary abscesses secondary to bronchiectasis.

FITZHERBERT, J. C.: *Management of hematemesis and melena.* (Med. J. Australia, April 15, 1950, 490-498).

148 cases of hematemesis or melena, or both combined, showed an overall mortality rate of 8.8 per cent, the rate for the peptic ulcer group being 7.3 percent. The mortality rates in the gastric ulcer group and duodenal ulcer group were 11.5 and 4.5 percent, respectively. Hemorrhage from chronic gastric ulceration carries a high mortality rate (22 percent in this series) which cannot be greatly reduced by conservative treatment. The basic indication for surgical intervention to control hemorrhage was bleeding in excess of 1500 c. c. in 24 hours. In older persons less bleeding should be permitted. The author judges the amount of bleeding from the amount of transfused blood needed to keep the hemoglobin reading at 70.

MOORE, A.: *Glucose tolerance curves before and after gastrectomy.* (Med. J. Australia, April 29, 1950, 563-566).

Glycosuria may occur after a normal meal in patients who have undergone subtotal gastrectomy, and this ought not to be mistaken for diabetes. Patients suffering from ulcer or cancer of the stomach yield glucose tolerance curves which tend to rise above normal and to be slow in returning to normal. About a month after operation the curves are of a similar nature but the return to normal is slightly more rapid. Three months after operation, low fasting levels are sometimes present and levels below 65 mgms. percent are more frequent in this group. In this group the blood sugar level may rise above 180 mgm. percent but usually falls to normal in two hours or less. The lowest levels of blood sugar do not necessarily follow the highest rises. It is suggested that the mucosa of the upper jejunum is adapted to a slower absorption, thus preventing the occurrence of abnormally high levels during the test. Apparently the type of diet consumed has no effect on the Maclean lag curve, provided the diet is adequate.

EFFLER, D. B.: *Complications of hiatus hernia.* (Cleveland Clin. Quart., 17, 2, 58-63).

Esophageal hiatus hernia is being recognized with increasing frequency, due to the work of the roentgenologists. The most troublesome complication of hiatus hernia is bleeding, occult or massive. Peptic ulcer may occur in the herniated portion of the stomach. When the herniated stomach displaces the heart to the right and the thoracic aorta to the left, we are most likely to have anginal-type pain produced, dyspnoea and back or shoulder pain. There may be a volvulus of the herniated portion of the stomach, occasionally with gangrene. Hiatus hernia should always be suspected when there is unexplained bleeding from the gastrointestinal system.

ROSSMILLER, H. R., BROWN, C. H. AND WHITMAN, J. F.: *Needle biopsy of the liver.* (Cleveland Clin. Quart., 17, 2, 64-71).

Needle biopsies (using "Vim" Silverman needles) were done on 50 patients with enlarged liver and biopsy with the needle under peritoneoscopic control on 25 patients without hepatic enlargement. Satisfactory specimens were obtained in 67 of the 75 cases. The biopsy procedure was helpful in 25 cases of cirrhosis in whom liver function tests and the clinical picture did not yield an accurate diagnosis. It often saved patients the expense and discomfort of laparotomy. In 3 patients the diagnosis of primary liver cell carcinoma was made by this means. The method is valuable in diagnosing malignant melanoma, hemochromatosis and Gaucher's disease.

WARD, E., PARKIN, T. W. AND HOWELL, L. P.: *Diabetes mellitus and Addison's disease: report of a case with normal urinary corticosteroids and high insulin requirement.* (Proc. Staff Meet. Mayo Clin., 25, 7, 145-149).

The authors report an unusual case in which Addison's disease developed in a male patient suffering from diabetes mellitus. While most diabetics with adrenal insufficiency show a marked sensitivity to insulin, this case did not, and, furthermore, he excreted normal amounts of corticosteroids in the urine. Probably this patient's adrenals continued to produce carbohydrate-active steroid hormones in spite of other evidences of cortical insufficiency. He presented hypotension, gastrointestinal symptoms, and marked skin pigmentation, almost collapsed on withdrawal of sodium, and made dramatic improvement on injection of adrenal cortex in aqueous solution, being placed on continued dosages of methyl testosterone and desoxycorticosterone by mouth, salt (5 gm. daily) and his usual insulin dosage.

KAY, A. W. AND SMITH, A. N.: *Effect of hexamethonium iodide on gastric secretion and motility.* (Brit. Med. J., Feb. 25, 1950, 460-463).

The authors found that hexamethonium iodide (a member of the homologous series of polymethylene-bistrimethyl-ammonium compounds) on intramuscular injection in doses of 100 mg. was the most effective drug yet available as an inhibitor of gastric secretion and motility, inasmuch as it reduced acid secretion to achlorhydria in peptic ulcer patients and produced complete ablation of gastric motility. It obviously acted as a blocker of the vagus for it negated the effects of insulin injection but did not counteract histamine which is considered to act directly upon the secreting cells of the stomach. Patients with ulcer pain gained complete relief for at least 5 hours following a single injection. Few unfavorable side effects were noted. Attempts are now being made (1) to procure a slowly-absorbed product and (2) to administer the drug by mouth.

ROSS, C. A. C.: *Direct microscopical examination of feces in infants.* (Brit. Med. J., Feb. 25, 1950, 465-467).

Direct microscope examination of fecal smears in 52 breast-fed infants showed that *Lactobacillus bifidus* was the predominant organism in 49. In direct smears from 46 artificially fed infants, lactobacilli were scanty or absent in 33. In fecal smears from 38 newly born infants, this organism was predominant in all those over 6 days old. Of 75 infants admitted to hospital with a diagnosis of enteritis, those showing a large proportion of Gram-negative organisms in their fecal smears were severely ill. A marked shift towards a Gram-negative flora is likely to indicate a severe enteritis with poor prognosis. Obviously this work emphasizes the importance of breast feeding from the standpoint of the infant's health and resistance to infection. The direct smear has distinct advantages.

FRIEDMAN, J. AND RIGLER, L. G.: *A method of double-contrast roentgen examination of the small intestine.* (Radiology, Mar. 1950, 54, 3, 365-379).

By employing a triple-lumen Miller-Abbott tube with two balloons, a portion of the small gut about 25 cms. long can be "fenced off", aspirated or injected with air or barium or both, and by such technique a special study of double-contrast can be made of an area suspected of containing an organic lesion. Changes in the mucosal pattern can be adequately visualized. The area from which bleeding is coming may be detected by testing the aspirated material with guaiac solution and then intensively studied. The method is useful in intestinal obstruction and, in general, seems to offer distinct advantages over the ordinary barium-by-mouth method.

HAWLEY, C. AND MITHOEFER, J.: *Ileal prolapse.* (Radiology, 54, 3, 380-385).

Prolapse of ileal mucosa into the cecum through the ileocecal valve is a rare condition. Two cases are reported, in each of which a filling defect in the cecum shown by barium enema examination was mistakenly interpreted as a polypoid tumor. In both cases, operation showed only prolapse of ileal mucosa into the cecum. A preoperative differentiation from more serious conditions (cancer, polyp, intussusception, etc.) cannot be made with certainty.

MACHT, S. H.: *Modified technic for cholangiography and use of a new contrast medium (Rayopake) for visualization of the biliary tree.* (Radiology, 54, 3, 421-423).

The author describes a modified method for delayed postoperative cholangiography with the patient in the exaggerated Trendelenberg position and with the use of rayopake (Hoffmann-LaRoche Co.) which has the advantage of high viscosity and radiopacity and will not flow rapidly out of the biliary tree. It also outlined non-opaque calculi more sharply than diodrast, although it does not delineate the finer biliary radicles as clearly. It has no toxic effects.

O'KEEFE, E. S.: *A high calorie diet in the treatment of diarrhea in infancy.* (Amer. Pract. and Digest of Treatment, 1, 3, 262-265).

In a group of infants suffering from diarrhea it was possible to prevent weight loss by using high caloric diets. This suggests, if it does not prove, that not all the intestinal tract is affected by the disease. Rather it would appear that the absorptive function remains unimpaired. The use of high caloric diet by the mouth represents not only an effective method of treating diarrhea in infants but it is much less laborious than parenteral feeding, and much more logical than the customary starvation regimes, because the food intake assists the body to produce antibodies to combat the infection. The author gives the patient one level tablespoonful of apple powder in three ounces of water before each milk feeding. This can be accomplished by the use of a nursing bottle, provided the hole in the nipple is sufficiently enlarged.

COHEN, S. G. AND CRIEP, L. H.: *Urticaria and angioedema in association with amebiasis.* (Amer. Pract. and Digest of Treatment, 1, 3, 246-252).

In a series of 28 patients with chronic urticaria of undetermined etiology, 19 were found to have associated amebiasis. The disease occurred in world war II veterans. These patients failed to respond to ephedrine, adrenalin and antihistaminic agents, but all of them improved following anti-amebic therapy. Had the stools not been examined, these cases would all have been regarded as neurotic. Since amebiasis is more common than usually believed in the general population, a new possible angle is provided for the study of the etiology of urticaria. Any present explanation of the association of urticaria with amebiasis must be purely speculative, but it appears most likely that the body of the host becomes sensitized to the proteins of E. histolytica.

DEARING, W. H. AND HEILMAN, F. R.: *The effect of aureomycin on the bacterial flora of the intestinal tract of man: a contribution to pre-operative preparation.* (Proc. Staff Meet. Mayo Clin., 25, 4, 87-102).

The authors have found aureomycin to be the most effective substance, in their experience, for removing bacteria from the intestinal tract of man. They employ 750 mg. four times daily for 3 or 3½ days. Nausea, when it occurs, is helped by eating. Care should be used in giving aureomycin to patients who have duodenal ulcer, as the authors have heard of 2 cases, not in their series, in which duodenal ulcer perforated after receiving aureomycin.

STEWART, G. T.: *Post-dysenteric colitis.* (Brit. Med. J., Feb. 18, 1950, 405-409).

Amebic dysentery, or less commonly, bacillary dysentery, may be followed by chronic colitis, supervening after the clearance of the original infecting organism. There is a non-ulcerative form, largely functional, which naturally gets better. Of the ulcerative forms, some respond to antibacterial treatment and some do not, the latter suggesting some relationship to idiopathic ulcerative colitis.

APPOINTMENT OF JOINT STUDY PANEL ON LIMITATION OF NUMBER OF DOSES IN CONTAINERS FOR INJECTIONS

At its organization meeting in New York on September 22, the U.S.P. Committee took action to invite the joint participation of the Committee on National Formulary and the Combined Pharmaceutical Contact Committee in studying the problems involved in limiting the number of doses in containers for injections. This action followed the postponement of the effectiveness of the U.S.P. XIV provision which was to limit the volume of injections in multiple-dose containers to ten U.S.P. Usual Doses. A similar action has been taken by the Committee on National Formulary with respect to N. F. items.

The Study Panel has now been made up. Dr. Justin L. Powers, Chairman of the Committee on National Formulary, has appointed Dr. W. Arthur Purdum, Chief Pharmacist, Johns Hopkins Hospital, and Dr. Hugo H. Schaefer, Dean, Brooklyn College of Pharmacy, to represent the National Formulary. Similarly, Dr. Frank O. Taylor, Chairman of the Combined Pharmaceutical Contact Committee, has appointed Mr. Edgar B. Carter, Abbott Laboratories, and Mr. Roland H. Noel, Bristol Laboratories, to represent the Contact Committee. For the U.S.P. Committee of Revision, Dr. Lloyd C. Miller, Director of Revision, has appointed Dr. George E. Farrar, Jr., Temple University School of Medicine, and Dr. Leslie N. Gay, Johns Hopkins School of Medicine. The chairmen of the three committees concerned will serve as ex-officio members of the panel.

The above-mentioned action of the U.S.P. Committee of Revision was taken following a report of a survey conducted by Dr. Taylor of the U.S.P. products seriously affected by the limitation. This revealed that some thirty-six manufacturers market thirty U.S.P. products, the packaging of which in one way or another exceeds the limitation of ten U.S.P. Usual Doses. In some cases the products are marketed in volumes corresponding to approximately fifty U.S.P. Usual Doses. This situation arises in part because some products have come to be used for indications requiring much larger amounts than the U. S. P. Usual Dose. Thus, there arises in this instance the question of whether the U.S.P. dosage statement should be revised or whether the trade practice should be altered.

A second problem revealed in Dr. Taylor's report concerns the several cases where the U.S.P. states no usual dose inasmuch as the dosage must be modified according to the needs of the patient by his physician.

Finally, an important aspect of the problem, which cannot be considered completely beyond the purview of the study, is the effect that the U.S.P. limitation automatically has upon non-official preparations.

The Study Panel will meet at an early date to extend the progress already made towards a solution of these problems. Constructive suggestions have already been received from many sources, but every helpful criticism will be welcomed by members of the panel. Particular attention will be paid to the advice of the practicing physicians on these questions.

A serious effort will be made to complete the study at the earliest possible date in order that the pharmaceutical manufacturers will have the benefit of knowing what will be required to comply with changes in the present official regulations, if such are made.

SQUIBB BULLETIN

The *Squibb Abstract Bulletin* is now available to individuals and institutions on a subscription basis at $25. a year, it has been announced by Dr. Geoffrey Rake, Director of The Squibb Institute for Medical Research and Medical Director of E. R. Squibb & Sons.

The *Bulletin*, now in its twenty-third year of publication, is issued weekly. Abstracts of articles from approximately 500 American and European journals in the fields of medicine, pharmacology, chemistry and biochemistry are included. Each weekly issue contains nearly 100 abstracts, and each gives some 115 title listings of additional papers sometimes with a brief indication of the contents. The abstracts represent those papers which are considered to be most important. An annual author index is published and each issue gives subject headings with individual entries.

Abstracting is unusually prompt; the bulk of the material appears in the *Bulletin* within three weeks after receipt of the journals in the Squibb library.

The staff of the *Bulletin* is headed by Winifred Sewell, Librarian, H. L. Alexander, Editor, and Jean L. Quigley, Assistant Editor. Four staff members are technically trained abstracters, all of whom read at least French and German. Various staff members also read Spanish, Italian, Portuguese, Danish, Norwegian, Swedish, Russian and Dutch.

"Although developed as a tool for Squibb research and development staffs, the *Squibb Abstract Bulletin* has grown to cover so wide a field that many outside institutions and individuals have found it helpful," Dr. Rake said. "Requests for individual copies or for the continuing series have reached such proportions, that we have decided to make the publication generally available. The subscription charge, while it is nominal and is not expected to make a significant contribution toward our total costs, will probably help to broaden the *Bulletin's* coverage and to increase its usefulness," he said.

Until this time circulation of the *Bulletin* outside of Squibb has been strictly limited to educational institutions and hospitals numbering about 250. In addition to circulation throughout this country, copies have gone to Argentina, Belgium, Brazil, Canada, Chile, China, Colombia, Cuba, England, Germany, Greece, India, Israel, Italy, Mexico, Panama, Peru, Philippine Islands, Puerto Rico, Sweden, and Uruguay.

The *Squibb Abstract Bulletin*, Dr. Rake said, can be subscribed to in multiple copies with $25. being the annual charge for the first copy and $15. for additional copies. Copies printed on only one side of the page and which are thus suitable for clipping are available at the same price.

CHLOR-TRIMETON MALEATE 8 MG. REPEAT ACTION TABLETS

Manufacturer: Schering Corporation, Bloomfield, New Jersey.

Active Constituent: Chlorprophenpyridamine maleate (1-para-chlorophenyl-1- (2-pyridyl)-3-dimethylaminopropane maleate, 8 mg.

Action: Repeat action is provided by two layers of Chlor-Trimeton maleate. 4 mg. in the outside coating is intended to produce immediate symptomatic relief lasting about 4

to 6 hours, and a special inner coating is designed to release another 4 mg. in the core after about 3 to 6 hours. Chlor-Trimeton maleate has markedly increased pharmacologic activity over all other available antihistamines.

Indications: Especially when longer effect from a single tablet is required, indicated for symptomatic relief of manifestations of allergic states, such as hay fever, vasomotor rhinitis, urticaria, allergic eczema, angioedema, serum sickness and drug sensitivity. Benefit may frequently be apparent from its use in atopic dermatitis, insect bites, migraine, pruritus ani and vulvae, and pruritus of nonspecific origin. It may be considered worthy of clinical trial in allergic headache, dermographism, gastrointestinal and physical allergy, neurodermatitis, poison ivy, tuberculous reactions, transfusion reactions and exanthem eruptions such as measles and chicken pox.

Dosage: Adults—One 8 mg. tablet at bedtime, or every 8 to 10 hours during the day. This special-coated tablet is designed for administration to adults only.

Packaging: Tablets of 8 mg., buff coated; bottles of 100 and 1000.

SIGNIFICANT ADVANCE IN ORAL ANTICOAGULANT THERAPY

Great impetus to the utilization of anticoagulant therapy in the treatment of coronary thrombosis and thromboembolic disorders is anticipated as a result of the announcement by the Geigy Company that Tromexan, a new orally administered anticoagulant, is now available for clinical use.

The older anticoagulant agents present certain well-recognized drawbacks—chiefly the problem of control to avert hemorrhagic action—and for these reasons the utilization of anticoagulant therapy has not been as widespread as it should be in light of the high incidence of coronary thrombosis and other thromboembolic disorders. An indication of the size of the problem is the estimated 600,000 fatalities reported annually due to coronary and thromboembolic disorders.

The new substance, Tromexan, it is anticipated on the basis of clinical findings already available in the literature, will eliminate many of the hazards now encountered in the other forms of anticoagulant therapy. The unique advantages of Tromexan noted by investigators in the United States and abroad are more rapid anticoagulant action, more predictable effect on prothrombin level, absence of dangerous cumulation and more favorable potency-toxicity ratio.

Studies at Cornell University—New York Hospital Medical Center have confirmed Tromexan's favorable clinical features. These studies have been extended to several leading medical centers under the auspices of the Committee on Anticoagulants of the American Heart Association.

Geigy Company, manufacturer of Eurax for scabies and Panparnit for Parkinson's disease, is the originator of DDT insecticides. Established in 1764, its leadership in organic research and synthesis has led to the development of original pharmaceuticals widely prescribed in virtually every country in the world.

NEW RICE CEREAL FOR INFANT MENUS

A new pre-cooked Rice Cereal, developed in response to medical recommendation, is being introduced for the nation's babies by Gerber Products Company.

Smooth and palatable, Gerber's Rice Cereal will provide variety, with valuable nutritives, for infants and toddlers with allergy problems, giving a wider choice of one-grain cereals.* The new cereal has been accepted by the A.M.A. Council on Foods and Nutrition.

The known digestibility of rice seems to make it a logical starting food for the very young. Like the other three Gerber's cereals, Rice Cereal is generously supplemented with essential B-vitamins and is packaged in the 8 oz. size.

*Gerber's new Rice Cereal is hypoallergenic and is therefore especially helpful for infants with wheat or oat allergy problems. Its B-vitamin supplementation is from rice bran extract plus crystalline thiamine, riboflavin and niacinamide.

DR. SEED NAMED EXECUTIVE AT RESEARCH INSTITUTE

Rensselaer, N. Y.—Mr. John C. Seed, formerly Chief of the Aerosol Section at the Army Chemical Center in Edgewood, Md., has been appointed executive assistant to Dr. Maurice L. Tainter, director of the Sterling-Winthrop Research Institute here. Dr. Seed's duties include liaison between the Institute and the medical profession.

A native of Rochester, Minn., he attended Princeton University and received his M. D. degree from Harvard Medical School in 1945. He interned at the Massachusetts General Hospital until entering the Army in April, 1946. In the Army, Dr. Seed supervised and conducted research at the Army Chemical Center. Upon release from the service he continued similar duties as a civilian employee until his arrival at the Institute.

TRIMETON MALEATE LOTION WITH PREPARED NEO-CALAMINE

Manufacturer: Schering Corporation, Bloomfield, New Jersey.

Active Constituents: Prophenpyridamine maleate (1-phenyl-1-(2-pyridyl) - 3 - dimethylaminopropane maleate), 2%; Prepared Neocalamine N. F.; Zinc Oxide U. S. P.

Indications: A bland, delicately scented, flesh colored lotion for the relief of itching due to poison ivy and poison oak, insect bites, sunburn, and other minor irritations of the skin.

Dosage: Apply locally three or four times daily. (For external use only).

Packaging: Bottles of 4 and 16 ounces.

NOTICE

Trade Name: NUPERCAINAL CREAM

Classification: Surface anesthetic

Manufacturer's Name: Ciba Pharmaceutical Products, Inc., Summit, N.J.

Formula: Water-washable base containing 0.5% NUPERCAINE (brand of dibucaine).

Description: A white, non-staining cream containing a local anesthetic.

Action: NUPERCAINAL CREAM acts on the peripheral nerve endings to block pain stimuli.

Uses: NUPERCAINAL CREAM provides immediate and prolonged relief from the pain of sunburn, minor burns and abrasions.

How Supplied: Tubes of 1 oz.

Administration: Applied to the skin liberally and with gentle rubbing will be absorbed into the tissue.

Prices: Druggist list—Tubes of 1 oz.—$6.00 doz. Fair trade minimum retail—Tubes of 1 oz.—$.75 ea.

Expert Skier...

DIETARY DUB!

He spent years learning to execute a slalom with perfect balance, yet gives little thought to balance in his diet. The end of a strenuous race finds him partaking of his usual one-sided fare: meat and potatoes—and more meat and potatoes. Salads and side dishes, which supply other essential vitamins, he all but ignores. Without realizing it, he is approaching the downhill slide to a subcritical vitamin deficiency.

Treatment of such deficiencies frequently calls for added B complex factors; for these cases, SUR-BEX proves a valuable adjunct to a corrected diet. Triple-coated SUR-BEX tablets are rich in vitamin B, yet pleasant tasting and easy to swallow.

When a lack of ascorbic acid is also apparent, prescribe SUR-BEX WITH VITAMIN C tablets. In addition to the potent B complex factors present in SUR-BEX these capsule-shaped tablets contain 150 mg. of ascorbic acid. Both products are supplied in bottles of 100, 500 and 1000 triple-coated tablets.

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Each SUR-BEX Tablet contains:

Thiamine mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid (as calcium pantothenate)	10 mg.
Liver fraction 2, N.F.	0.3 Gm. (5 grs.)
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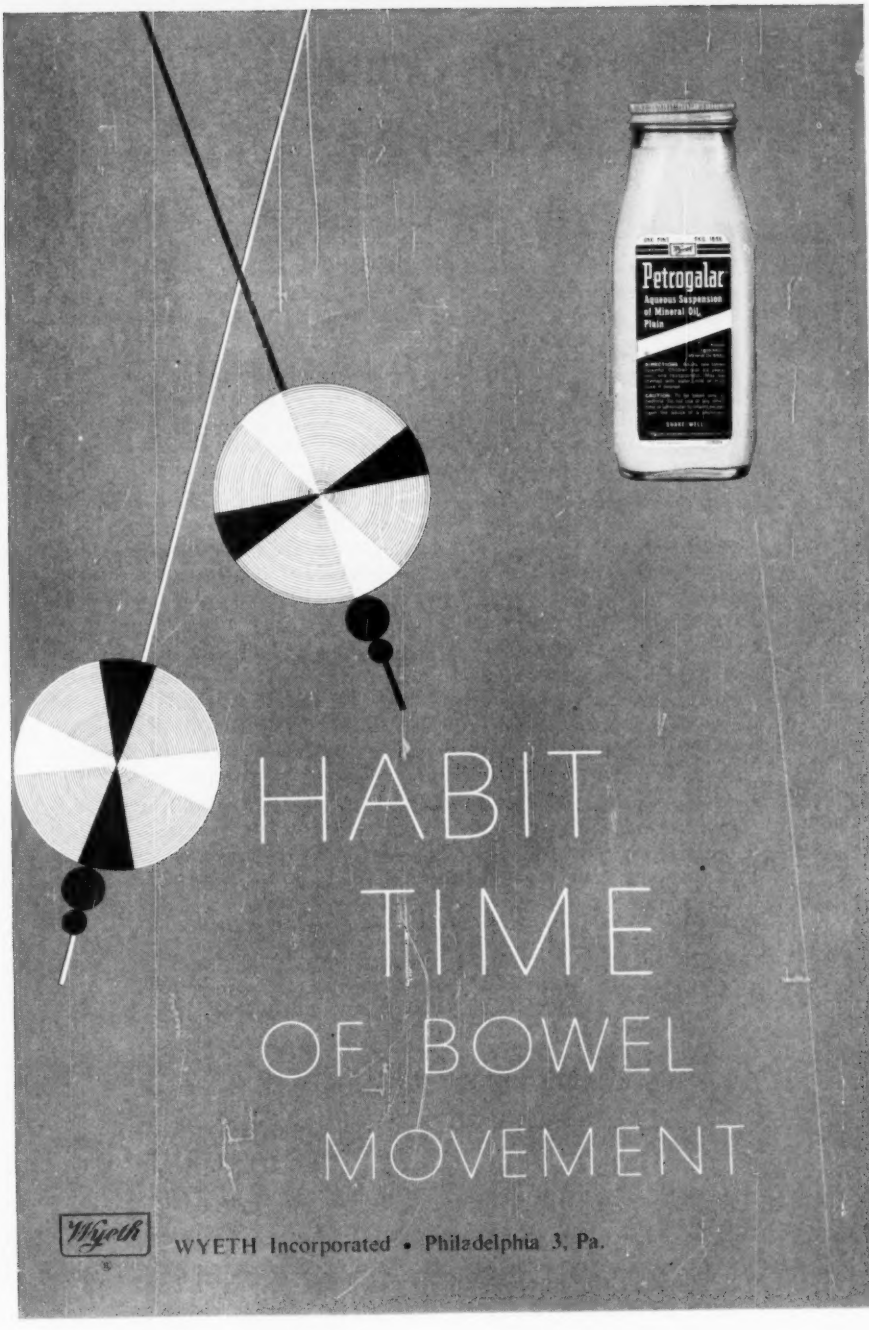
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High Vitamin B_{12} Content... Another Reason for Liberal Meat Intake

According to rapidly accumulating clinical and laboratory observations, the daily ingestion of liberal quantities of meat can effect profound physiologic benefits due to the significant content of vitamin B_{12}, not only in liver and kidney, but also in muscle meats.

Muscle meat is a good source of the newly isolated vitamin B_{12}; liver and kidney are especially high in their vitamin B_{12} content, while plant foods are negligible sources of this nutrient.[1] By rat assay, the minimum amounts of vitamin B_{12} in muscle meat range from 0.5 to 3 mcg. per 100 Gm.; minimum values for beef liver and kidney are 15 and 20 mcg., respectively.[2]

B_{12} is among the most potent of known microbiologically active substances.[3] Animal studies indicate that it increases the ability of the normal mammal to utilize protein.[4] With a high protein diet, 0.01 mcg. of vitamin B_{12} per day was found to increase significantly the growth rate of B_{12} deficient rats. In another study, growth response of B_{12} depleted rats was proportional to the B_{12} in the ration within the critical range of 0.025 to 0.1 mcg. per rat day.[5]

About 1 mcg. of vitamin B_{12} daily, administered intramuscularly, constitutes an effective dose in pernicious anemia. In a recent clinical study of young children manifesting vitamin B_{12} deficiency as evidenced by malnutrition and growth failure, oral administration of 10 mcg. of vitamin B_{12} daily for eight weeks induced marked responses in growth; notable increases in vigor, alertness and better general behavior; and improved appetite.[6]

Here again is further evidence of the broad, over-all nutrient contribution meat makes to the dietary. Eaten two or three times daily, it supplies not only generous amounts of high quality protein, but also significant quantities of vitamin B_{12} and other essential B complex vitamins, and of iron.

---

(1) Schweigert, B. S.: Significance of Vitamin B_{12} and Related Factors, J. Am. Dietetic Assoc. *26*:782 (Oct.) 1950.

(2) Lewis, U. J.; Register, U. D.; Thompson, H. T., and Elvehjem, C. A.: Distribution of Vitamin B_{12} in Natural Materials, Proc. Soc. Exper. Biol. & Med. *72*:479 (Nov.) 1949.

(3) Shorb, M. S.: Activity of Vitamin B_{12} for the Growth of Lactobacillus lactis, Science *107*:397 (Apr. 16) 1948.

(4) Hartman, A. M.; Dryden, L. P., and Cary, C. A.: The Role and Sources of Vitamin B_{12}, J. Am. Dietetic Assoc. *25*:929 (Nov.) 1949.

(5) Frost, D. V.; Fricke, H. H., and Spruth, H. C.: Rat Growth Assay for Vitamin B_{12}, Proc. Soc. Exper. Biol. & Med. *72*:102 (Oct.) 1949.

(6) Wetzel, N. C.; Fargo, W. C.; Smith, I. H., and Helikson, J.: Growth Failure in School Children as Associated with Vitamin B_{12} Deficiency—Response to Oral Therapy, Science *110*:651 (Dec. 16) 1949.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute
Main Office, Chicago...Members Throughout the United States

In palatable liquid dosage, it is now possible to provide complete and effective medical protection for the peptic ulcer patient.

ALZINOX MAGMA

WITH PHENOBARBITAL AND HOMATROPINE METHYL BROMIDE

combines:

1. **the prolonged antacid—*but not alkalizing*—action of the true buffer, Alzinox;**
2. **the sedative action of phenobarbital;**
3. **the antispasmodic effectiveness of homatropine methyl bromide.**

In completely dispersible "Magma" form to insure coating of the ulcer crater

ALZINOX MAGMA WITH PHENOBARBITAL (1/8 gr. per 5 cc.) *and* HOMATROPINE METHYL BROMIDE (1/100 gr. per 5 cc.)—bottles of 8-oz.
Average dose: one to two teaspoonfuls two hours after meals and at bedtime.

Also: ALZINOX MAGMA (*plain*): 0.5 Gm. (7.7 gr.) per 5 cc.—bottles of 8-oz.
ALZINOX TABLETS with Phenobarbital (1/4 gr.) and Homatropine Methyl Bromide (1/100 gr.)
ALZINOX TABLETS (*plain*)—0.5 Gm. (7.7 gr.)—bottles of 100 and 500.

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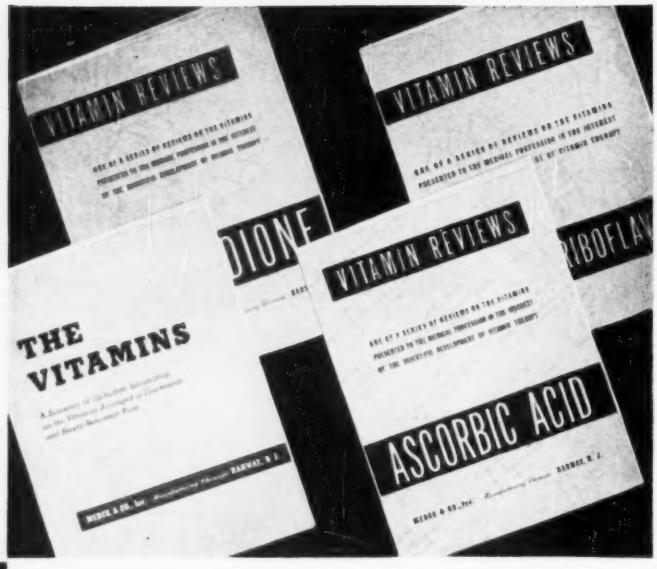
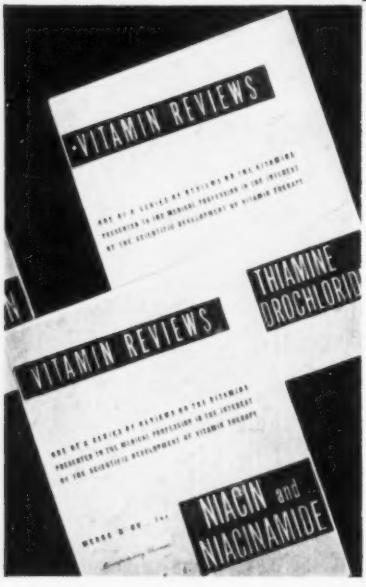
From Merck & Co., Inc. —where many of the individual vitamins were first synthesized.





These six Merck *Vitamin Reviews* are yours for the asking while the editions last. These concise reviews contain up-to-date, authoritative facts and can be most useful for quick reference. Please address requests for copies to Merck & Co., Inc., Rahway, N. J.

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- Factors that produce avitaminosis.
- Signs and symptoms of deficiency.
- Daily requirements and dosages.
- Distribution in foods.
- Methods of administration.
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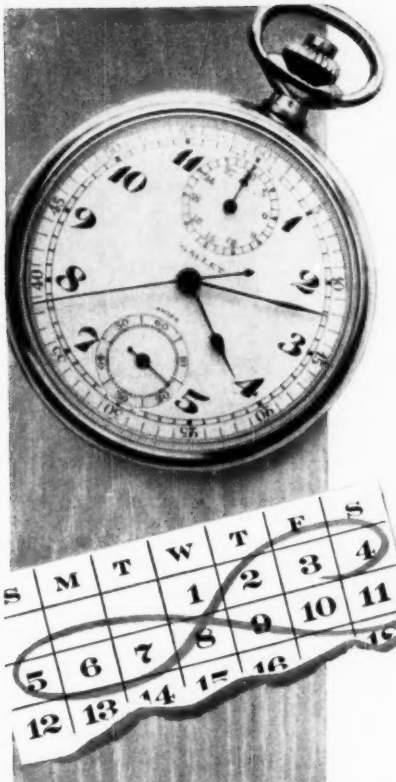

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of ulcer pain in minutes

Because Creamalin is *amorphous* aluminum hydroxide, the most soluble, nonabsorbable gel ever prepared,[1] it neutralizes fast — up to twelve times its volume of N/10 HCl in less than 30 minutes.

Relief with Creamalin is fast also because it is a *reactive* aluminum hydroxide with greater acid-combining power.[2]

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in 7 to 10 days

Because Creamalin is *acid-soluble* aluminum hydroxide, the most effective form for prolonged neutralization of gastric acidity,[1] ulcers treated with Creamalin often heal within 7 to 10 days.

Healing is fast also because Creamalin has a prolonged antacid effect which inhibits tissue-digesting pepsin activity. Tablets or liquid.

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1. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Co. 7th ed., 1948, p. 938.
2. Batterman, R. C., and Shay, H., Gastroenterology, 9:141, Aug., 1947.

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NOTED EDUCATOR NAMED TO RED CROSS BLOOD POST

Washington, D. C.—Dr. Russell Landram Haden, medical educator and recently head of the Department of Medicine at the Cleveland, O., Clinic, has been appointed medical director of the Red Cross National Blood Program, Gen. George C. Marshall, the organization's president announced today.

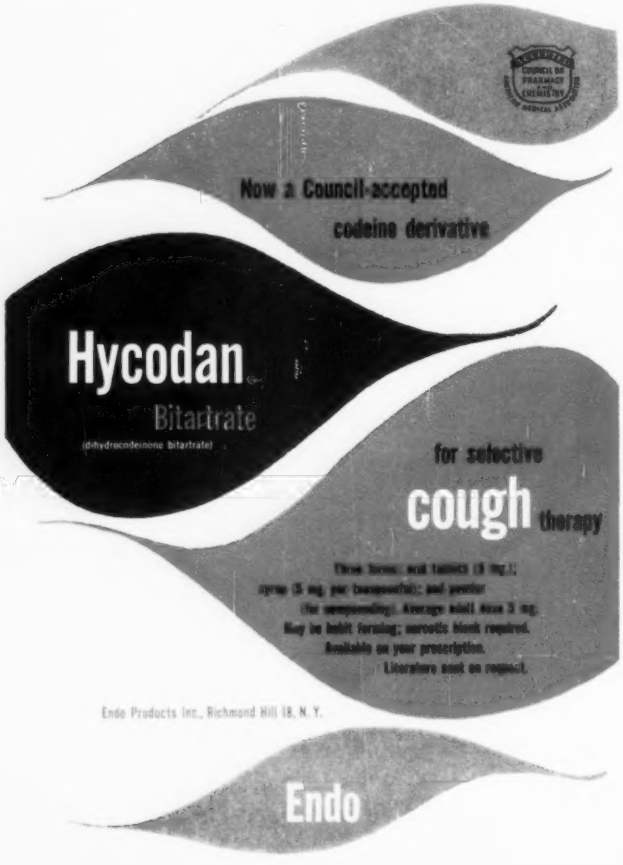
Dr Haden will direct the medical aspects of the blood program as it is expanded to provide blood, plasma and other derivatives for the nation's hospitals and for military and civil defense needs. He will work with Dr. Ross T. McIntire, chairman of the blood program's committee on medical policies and procedures. This committee of leading surgeons and hematologists is supervising the planning and development of Red Cross blood collection centers and the coordination of the country's private and institutional blood banks in carrying out the responsibilities assigned Red Cross by the military and defense authorities.

A native of Virginia, Dr. Haden graduated from Johns Hopkins Medical School. Following a residency at Johns Hopkins Hospital he became Director of Laboratories in the Henry Ford Hospital, Detroit. For a number of years he was professor of experimental medicine at the University of Kansas. He has been associated with the Cleveland Clinic since 1930.

Holder of a gold medal award from the Radiological Society of America, Dr. Haden is author of "Clinical Laboratory Methods" and "Principles of Hematology" and is a contributor to numerous medical journals. He is a member of the American Medical Association, a fellow of the American College of Physicians and a member of the American Society of Clinical Investigation and other professional organizations.

The Red Cross national blood program is now operating 35 regional blood collection centers and is in process of adding 7 more to the network. Civil Defense centers for the procurement of blood to meet the demands of defense preparedness are also being established in a number of metropolitan areas.

Dr. Haden succeeds Dr. Louis K. Diamond, Boston Hematologist and a member of the Harvard Medical School faculty, who resigned to return to his duties at Harvard and at Children's Hospital where he is director of the blood bank and research laboratory.



NOTICE

Hoffmann-La Roche Inc. recently announced that its multi-vitamin specialties—Vi-Penta Drops and Perles, Supradin and Cal-C-Tose—now contain *synthetic* vitamin A palmitate. The use of synthetic vitamin A—an achievement of the Roche Research Laboratories—eliminates fishy odor and taste, and obviates the possibility of allergy to fish liver oils. Roche is now manufacturing synthetic vitamin A palmitate and acetate "by the ton," supplying pharmaceutical manufacturers and food processors.

American Journal of Digestive Diseases

Volume 17

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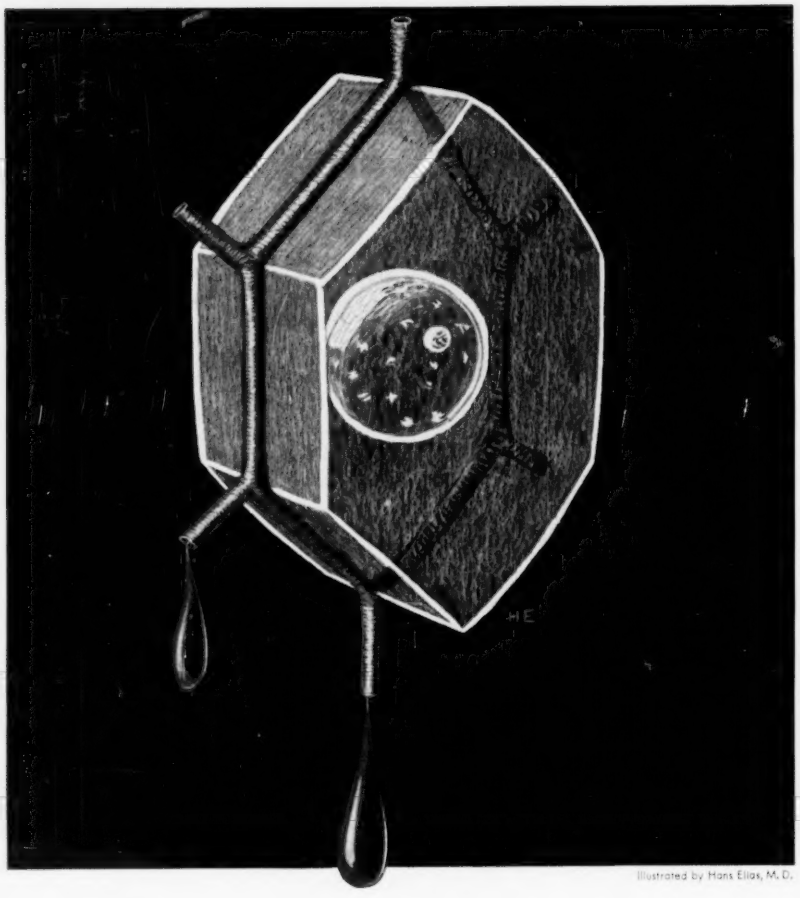

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